

THE AMERICAN JOURNAL OF PATHOLOGY

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VOLUME XX

1944

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TRANSPLANTABLE OSTEOGENIC SARCOMAS INDUCED IN RATS BY FEEDING RADIUM*

CHARLES E. DUNLAP, M.D. (*Department of Pathology, Harvard Medical School*) and JOSEPH C. AUB, M.D. (*John Collins Warren Laboratory of the Harvard Cancer Commission and the Harvard Medical School*), Boston, Mass.; and ROBLEY D. EVANS, Ph.D., and ROBERT S. HARRIS, Ph.D. (*Massachusetts Institute of Technology*), Cambridge, Mass.

Radium poisoning came into prominence as an important industrial hazard with the reports by Hoffiman,¹ Castle, Drinker and Drinker² and Martland and co-workers³⁻⁶ on the fate of employees in the luminous dial industry in New Jersey. The girls who were employed to paint the figures on clock and watch faces used a paint consisting of zinc sulfide rendered luminous by the addition of 1 part in 40,000 of radium, mesothorium and radiothorium. Prior to the recognition of the danger involved, these workers were in the habit of bringing their brushes to a sharp point by drawing the bristles between their moistened lips, and thus ingested each day a small amount of radioactive material. Deposits of radium within the body may be acquired in other ways⁷ but the luminous paint and dial industry, in spite of modern safety measures, still presents the greatest hazard.

Radium is similar in many ways to calcium and to lead and appears to follow the same metabolic pathways within the body.⁸⁻¹⁰ When radium is ingested most of it passes through the intestinal tract and is excreted with the feces. The small amounts which are absorbed are at first distributed in the soft tissues but are soon transferred to bone. In human cases of chronic poisoning practically all of the radioactive material is contained in the skeleton.⁷ In like fashion, Thomas and Bruner¹⁰ found that 99 per cent of the retained radium in rats was deposited in bone 2 to 8 months after injection. The exact mode of deposition is not known, but it is quite possible that radium substitutes for calcium in the formation of bone salts. The early site of skeletal deposition is in the delicate spicules of trabecular bone, but subsequently a more even distribution between cortical and trabecular bone is attained^{8,11} as has been shown for other heavy metals.¹² Deposits of radium in trabecular bone are fairly easily mobilized but when trans-

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ferred to dense cortical bone they are relatively stable, exchange is sluggish, and excretion is minimal.⁸ Early in the course of human poisoning excretion may amount to as much as 1 per cent of the total body deposits each day, but with the passage of time it falls to levels as low as 0.005 per cent a day.^{8, 10}

The total body content of radioactive material in persons who have died of radium poisoning has ranged from 2 to 180 μg . (micrograms).^{7, 13} It seems clear that such small quantities do not act as chemical poisons but as sources of radiant energy. The tissue damage results from the cumulative effects of constant exposure to alpha, beta and gamma radiation. Since alpha particles have little ability to penetrate tissues they are quickly absorbed and exert a concentrated injurious effect in the immediate vicinity of the radium deposits. They are, therefore, more effective in producing local tissue damage than the more penetrating beta and gamma radiations and are chiefly responsible for the ultimate lethal action of minute deposits of radium in the body.

Martland¹³ has reported in considerable detail the clinical course of radium poisoning and the pathological findings as seen in a group of dial painters. The principal symptoms reflect damage to the bones and bone marrow, as would be expected from the selective localization of radium in the skeleton. Heavily poisoned persons suffered from leukopenic anemias and necrosis of the bones of the jaw. Others remained in apparent good health for months or years after exposure and then developed chronic, crippling bone lesions or "radiation osteitis." The lesions were widely distributed over the skeleton and were characterized roentgenologically by patchy areas of increased and of decreased bone density. Pathologically the bone marrow in these areas showed immaturity and regenerative hyperplasia with occasional areas of aplasia and fibrosis. The most remarkable feature of Martland's series of cases was that 5 osteogenic sarcomas occurred among 18 persons who died from radium poisoning.

Attempts to reproduce the main features of radium poisoning in laboratory animals have met with considerable success. In general the radium has been introduced by injection rather than by feeding and the doses have often exceeded the range covered in cases of human poisoning. The blood and bone marrow changes seen in human beings have been reproduced and occasional osteogenic sarcomas have been obtained. A number of brief reviews are available on animal experiments¹⁴⁻¹⁶ as well as several on human poisoning and its treatment,^{7, 8, 13} but only a few of the more pertinent animal experiments will be cited here.

Thomas and Bruner¹⁰ injected 8 rats subcutaneously with doses of

40 to 60 $\mu\text{g.}$ of radium chloride. The animals retained an average of 25 per cent of the radium and showed progressive deterioration of the peripheral blood picture. At autopsy, 183 to 258 days after the first radium injection, 99 per cent of the retained radium was found in the bone ash. Hyperplastic marrow was present in the mid-shaft of the long bones and aplastic marrow at the ends. The bones were fragile and regions of necrosis were present. The spleen and lymph nodes showed atrophy, hemosiderosis and hematopoiesis. One rat developed motor disturbance of the hind legs shortly before death, but no tumor was discovered in any of the animals.

Sabin, Doan and Forkner¹⁶ poisoned 9 rabbits with repeated intravenous injections of radium or of mesothorium. One rabbit received a total of 70.4 $\mu\text{g.}$ of radium and died with osteogenic sarcoma of the humerus 18 months after the first injection. A second osteogenic sarcoma was found in a rabbit which had received 46.2 $\mu\text{g.}$ of mesothorium over a period of 11 months. Two other rabbits in which no tumors were found developed "marked weakness of the muscles or paralyzes" shortly before death.

One of the few animal experiments in which radioactive substances were fed rather than injected was carried out by Rosenthal and Grace.¹⁵ Four rabbits were fed radium sulfate by dropper three times daily for 90 days, to a total dose of 100 $\mu\text{g.}$ per animal. The animals survived 6, 15, 16 and 21 months respectively after the first radium feeding. Abscesses of the jaw, osteoporosis, newly formed subperiosteal bone and spontaneous fractures were observed but no tumors. Terminal paralysis of the hindquarters developed in one animal and was attributed to spontaneous fracture of a vertebra.

Martland's¹³ view that the damage suffered by dial painters was due almost entirely to alpha radiation, while beta and gamma radiations were negligible factors, is probably correct. However, no satisfactory evidence has yet been educed that different kinds of ionizing radiation produce qualitatively different biological effects. The observed differences have been quantitative and are explainable on the basis of variations in the intensity and distribution of ionization in different parts of the body. In animal experiments, gamma radiation, as well as mixed beta and gamma radiation, have been shown capable of inducing osteogenic sarcoma.

Ross¹⁷ implanted a platinum tube containing 0.1 mg. of radium under the periosteum of the rib of a rabbit. Two years later the tube was found encased in a large mass of osteogenic sarcoma. The wall of the platinum tube had a thickness of 0.55 mm., which is sufficient to filter off all the alpha radiation and practically all the beta radiation.

Her inference that the tumor resulted from exposure of bone and periosteum to gamma radiation appears to be justified. Schürch and Uehlinger,¹⁸ in a similar experiment, obtained an osteogenic sarcoma of the jawbone of a rabbit 1½ years after the subperiosteal implantation for 20 days of a platinum needle containing 1 mg. of radium. Hellner¹⁹ produced osteogenic sarcoma in the knee of a rabbit by the external application of a platinum-iridium tube containing radium.

Combined beta and gamma radiation was effective in the hands of Lacassagne and Nyka.²⁰ Osteogenic sarcomas were induced in the region of the sella turcica in 3 of 11 rabbits that survived over 1 year after the implantation of glass radon tubes in the hypophysis. The induction times of the tumors were 14, 13 and 12 months, and the strengths of the radon tubes were 0.69 mc., 1.08 mc. and 0.83 mc. respectively. The alpha particles from radon do not penetrate the wall of an ordinary glass capsule, so that the tissues of these rabbits were exposed to mixed beta and gamma radiation. The total doses used were much smaller than might appear since radon has a half-life of less than 4 days and emits only 133 mc. hrs. (millicurie-hours) of radiation in the total decay of one initial millicurie. The animal exposed to 0.83 mc. thus received a total dose of only 110 mc. hrs. A comparable dose could be delivered by exposing the animal to 1 mg. of radium for 110 hours.

The studies to be reported in this paper concern the fate of rats given radium by mouth, thus duplicating the mode of exposure to which the radium dial painters were subjected.

MATERIALS AND METHODS

Thirteen male Wistar rats, 5 months old, were each fed a total of 100 μ g. of radium chloride. The stock radium solution contained 1500 μ g. of radium taken up in 13 cc. of glycerine and 26 cc. of normal saline solution. Each rat was fed 3 drops of this solution daily for a period of 20 days. Detailed measurements of the retention and excretion of radium will be reported in a separate communication.²¹ It will suffice to say that about 95 per cent of the radium had been excreted by the tenth day after the final feeding and that an average of 2 μ g. remained in the body of each rat at the end of 10 months. All surviving animals, together with 2 controls, were x-rayed on October 31, 1941, 10 months after the radium feeding, and no significant changes in the skeletons were seen. Whenever an animal appeared moribund, it was killed with ether and autopsied.

Representative tissues were fixed in acetic acid-Zenker's solution, stained with eosin and methylene blue, phosphotungstic acid-hema-

toxylin, and Giemsa stain and examined microscopically. Whenever a tumor was found, fragments were transplanted subcutaneously into other rats.

Two of the primary tumors and a number of the transplanted tumors were assayed chemically for alkaline phosphatase activity and several were selectively stained for alkaline phosphatase by the method of Gomori.²²

RESULTS

None of the rats showed objective signs of disease during the first 8 months of the experiment, but then, one by one, 9 of them developed paralyzes of the hindquarters and the others became progressively emaciated and cachectic.

Autopsy Findings

The important features of the autopsies are summarized in Table I. The outstanding observation was that 9 of the 13 rats developed osteogenic sarcomas in time intervals of 253 to 426 days after the first radium feeding. The average induction time of the tumors was 365 days. The primary growths were in the vertebrae in 7 rats and in the pelvic bones in 2. One of the vertebral tumors was cervical, 3 were thoracic and 3 lumbar. All of the growths were so situated that they either had, or might have, exerted pressure on the spinal cord or major nerve roots (Fig. 1), thus explaining the terminal paralyzes that occurred in all but 1 of the tumor-bearing rats. However, 1 rat which had no tumor developed paralysis of the hind legs.

Metastases were found at autopsy in 2 of the 9 rats. In 1, the pelvic lymph nodes were invaded from a tumor primary in the ilium. In the other a primary sarcoma of the third thoracic vertebra was associated with a solitary nodule of bone-forming tumor in the lower pole of the spleen. Since the spleen has no afferent lymphatics, the splenic metastasis must have been blood-borne, whereas lymphatic spread was probably responsible for the lymph node metastases.

All of the tumors were so similar in gross and histological appearance that they may be described together. Grossly they were firmly attached to bone and extended as nodular projections into the surrounding soft parts. Although the borders were sharply defined there was no plane of cleavage between muscle and tumor. When there was extension into the spinal canal or thoracic cage, the tumors did not break through the lining membranes but presented as smooth, pale pink, epidural or subpleural masses (Fig. 1). All of the growths were hard centrally but carried a superficial layer of soft, pink, cellular tissue. The consistency was rigid, gritty and granular but never as hard as that of mature bone.

TABLE I
Pathological Changes in Rats Poisoned with Radium

Animal no.	Survival time after feeding radium (days)	Osteogenic sarcoma	Location of primary tumor	Bone marrow changes			Bone changes	
				Hypoplasia	Immaturity	Hemosiderin	Necrosis	New bone
25630	253	+	Vertebrae, T. 3, 5, 6 Vertebrae, C. 5, 6, 7	++	++	++	++	++
25631	318	+		++	++	++	++	++
25632	398	+	Both ilia Vertebra, L. 1	++	++	++	++	++
25633	398	+		++	++	++	++	++
25634	306	o	Vertebrae, T. 1, 2	++	++	++	++	++
25635	426	+		++	++	++	++	++
25636	289	o	Left ilium	++	++	++	++	++
25637	388	+		++	++	++	++	++
25638	305	o	Vertebra, L. 2	++	++	++	++	++
25640	418	+		++	++	++	++	++
25641	263	+	Vertebra, T. 3 Vertebra, L. 4	++	+	++	++	o
25642	419	+		++	+	++	++	+
25643	334	o		++	+	++	++	+
Controls								
25644	334	o		o	o	o	o	o
35647	530	o		o	o	o	o	o

Microscopically the neoplasms showed only minor individual variations (Fig. 2). They were all continuous with normal bone, often showing erosion or destruction of the cortex and growth within as well as outside the marrow cavities. It was impossible to determine in most instances whether they were of periosteal or endosteal origin. The advancing border of the tumor was made up of a compact mass of fusiform, stellate, or oval cells with a little pink, homogeneous, intercellular substance. Mitotic figures were present in considerable numbers and occasional tumor giant cells were seen. On passing from the periphery toward the central portion of the tumors pink-staining intercellular substance began to appear in greater quantity between tumor cells, ill defined at first but soon passing over into well-formed neoplastic bone. In the more mature regions a single layer of tumor cells covered the surface of each spicule of bone and closely resembled a row of normal osteoblasts. Calcium stains showed the central portions of each spicule of newly formed bone to be well calcified while the margins were apparently made up of uncalcified osteoid substance. The deeper portions of some of the growths contained large areas of degeneration with death of all cells but no evidence of hemorrhage or inflammation. No cartilage was present in the tumors. The metastatic nodules, found once in the lymph nodes and once in the spleen, were indistinguishable structurally from the primary growths. Two of the primary tumors were more anaplastic than the other seven and showed greater local invasiveness of muscle and smaller amounts of neoplastic bone formation.

The vertebral bone showed remarkable changes even in those regions uninvolved by tumor. In every animal there were patchy areas of sterile bone necrosis characterized by an absence of living osteocytes in the bone lacunae. The entire thickness of the cortex was often necrotic in addition to many spicules of trabecular bone in the marrow cavity. Although osteoclasts were rarely found, the necrotic bone usually showed irregularly scalloped regions of resorption along its free margins and sometimes the apposition of a surface layer of new living bone of fibrillar structure (Fig. 3). Poorly formed spicules of new bone were present in the vertebrae of all but 1 of the animals (Fig. 4). As a rule they extended longitudinally into the marrow cavity from the bony plate at one end of a vertebra. The osteocytes of the new bone were elongated and the matrix structure was loose and fibrillar. Some areas were acellular, suggesting that necrosis had taken place even in the newly formed bone. The old bone trabeculae in the vertebrae were coarse and irregularly thickened (Fig. 1), particularly in regions of

bone necrosis, as though the normal processes of bone resorption had been impaired.

Similar areas of bone necrosis with periodontal suppuration but without new bone formation were found in the mandible or maxilla in all of the 4 experimental animals in which the jaw bones were examined. The periodontal suppuration is of doubtful significance since a somewhat similar change was found in 1 of the controls. The explanation may lie in the fact that the animals were fed throughout the experiment on a diet of soft, ground food which furnished little exercise for the teeth and gums.

In addition to the changes in the bone itself, the bone marrow of all the experimental animals showed extensive hypoplasia and atrophy. In the vertebral bodies most of the surviving cells were gathered in the central portion of the marrow cavity while the peripheral portions showed extensive fatty aplasia (Fig. 5). In other parts of the skeleton the process was not so uniform and irregular regions of atrophy or hypoplasia alternated with more cellular regions. In the atrophic regions the marrow was replaced by fat cells together with a few scattered macrophages and stellate mesenchymal cells. Only slight fibrosis was present and very little of the "gelatinous edema" or mucoid degeneration which has been described in radiation damage to bone marrow.^{13, 17} More striking were the deposits of hemosiderin in the bone marrow of all of the animals examined. In the cellular portions of the marrow little or no hemosiderin was apparent and the heaviest deposits were present in macrophages between the fat cells of the atrophic regions. The only consistent abnormality of the surviving marrow cells was generalized immaturity. In some animals the proportion of erythroblastic and myeloblastic cells was normal while in others cells of one or the other series predominated. The number of megakaryocytes was reduced in proportion to the other marrow elements. Evidences of active cell destruction were not seen in any of the animals nor were areas of hyperplastic marrow encountered.

The spleen showed changes in all of the animals, fairly uniform in character, but varying in degree. In all cases the number of lymphocytes was reduced, the malpighian bodies were small and the total bulk of the spleen was slightly reduced. No fibrosis was apparent but hemosiderin deposits were abundant, both free and within phagocytic cells. Active centers of erythropoiesis were present in most instances. The lungs, liver, kidneys, testes, spinal cord and intestinal tract showed no constant changes attributable to radiation.

The significant histological changes, apart from the tumors, may be summarized briefly as follows: patchy sterile necrosis of bone with

atypical new bone formation; focal atrophy, hypoplasia, immaturity and hemosiderosis of the bone marrow; atrophy and hemosiderosis of the spleen with focal erythropoiesis.

Tumor Transplants

Attempts to transplant the tumors yielded several interesting results. The experimental animals belonged to the Wistar strain, but at the time of the first autopsies no other Wistar rats were available and the tumors were transplanted to stock rats. All of the transplants failed to grow with the single exception of one in an animal which had been irradiated 3 days previously.* The radiation was given in an attempt to favor the successful growth of an heterologous tumor transplant pursuant to reports of such action by Clemmesen.^{23, 24}

The tumor grew slowly for 3½ months, reaching a diameter of 1 cm. Roentgenographs taken at this time showed a heavily calcified nodule. A portion of the tumor was then excised under ether anesthesia and transplanted to 6 young Wistar rats. The original transplant has since remained static and is still present as a hard, subcutaneous nodule, 5 mm. in diameter, 16 months after transplantation. Portions of this tumor transplanted to the original Wistar strain grew progressively and reached diameters of several centimeters in 3 months. At autopsy 2 of these rats had extensive metastases of bone-forming tumor in the lungs. The tumor has now been carried through 7 serial generations of transplants. About 50 per cent "takes" are obtained and palpable nodules appear 1 to 2 months after transplantation. Occasionally a transplant which has apparently failed to take will begin to grow after a latent period of over 6 months. Pregnancy appears to accelerate growth. Once established, the tumors grow slowly and do not kill their hosts for a matter of 3 to 6 months. Death is usually caused by extensive central necrosis and ulceration of the transplant. Throughout a period of over a year of serial transplantation this tumor has retained its original histological characteristics and its ability to form bone.

Two other primary tumors were successfully transplanted to young Wistar rats but neither has been carried beyond the first generation.

Phosphatase Studies

Since a high concentration of alkaline phosphatase has been consistently demonstrated in human osteogenic sarcomas,²⁵ similar studies were made on the rat tumors. Chemical assays of alkaline phosphatase

* The treatment consisted of 1,000 r. of roentgen rays to a 5 by 5 cm. portal at 200 kv., 8 ma., 20 cm. skin-target distance and 0.25 mm. Cu filter, kindly administered by Dr. Milford Schulz.

activity were made on portions of the original neoplasms from rats 25640 and 25642 as well as on several rats with second, third and fourth generation transplants. The method employed was that of Martland and Robison²⁶ as modified by Franseen and McLean.²⁵ The results as summarized in Table II show that the rat sarcomas, like their human counterparts, have a high phosphatase content and that the phosphatase level is maintained in the transplanted tumors. The two sarcomas which were analyzed for calcium and phosphorus contained less of these minerals than is present in mature bone (Table II) but about the same amount as is found in the deer antler during the early stages of calcification.²⁷

TABLE II
Alkaline Phosphatase and Mineral Content of Osteogenic Sarcomas in Rats

	Alkaline phosphatase	Calcium	Acid-soluble phosphorus
	<i>Kay units</i>	<i>mg./gm. of fresh tissue</i>	<i>mg./gm. of fresh tissue</i>
Normal rat bones			
Vertebrae	15-26		
Femur (shaft)	12-13		
Femur (head)	18		
Osteogenic sarcomas			
2 Primary tumors	49.2-88		
3 Second generation transplants	66.3-88.2	29.0	13.9 (74% moisture)
1 Third generation transplant	75.3		
3 Fourth generation transplants	43.7-61.5	32.8	14.5 (53% moisture)

In order to observe the minute distribution of phosphatase in and around the tumors, alkaline phosphatase stains of microscopical sections were made according to the ingenious method of Gomori.²² Because of the high phosphatase content, all of the osteogenic sarcomas stained very darkly, but the enzyme appeared to be most heavily concentrated in the tumor cell nuclei. The enzyme was confined rather sharply to the neoplasm and showed very little diffusion into adjacent normal tissues (Fig. 6).

Tissue Cultures

Small fragments of two primary osteogenic sarcomas were explanted in tissue culture by Dr. Austin M. Brues. Good growth was obtained in both cases by the third day, but attempts to transplant the cultured fragments back into rats were not successful. Tissue stains failed to show any phosphatase in the new cells which had proliferated about the borders of the explant, although the enzyme was still stainable in the explant itself.

DISCUSSION

The histological changes observed in these 13 rats, following the ingestion of radium, have been described in some detail since they parallel so closely the pathological findings of radium poisoning as seen in the New Jersey dial painters. The outstanding difference has been the uniform finding of hypoplastic bone marrow in the rats, whereas many of the dial painters had a hyperplastic, regenerative marrow.

The difference may be due to the fact that the dose of radium which the rats retained throughout the experiment was approximately 2 μg . per animal and was thus considerably greater in proportion to body weight than in the dial painters whose total body content ranged from 2 to 180 μg .^{7, 13} In both the human beings and the rats a prolonged period of apparent good health was followed by skeletal changes and the ultimate development of a high percentage of osteogenic sarcomas. Profound damage to blood-forming organs was found at autopsy, together with widespread necrosis of bone. Many of the osteogenic sarcomas in the rats were found in the vertebral bodies, while in the human beings they were in the pelvis, lower extremity and elsewhere. The difference in distribution may be accidental but might be related to the fact that the epiphyses in the rat remain open throughout life and bone growth continues to a slight extent even in the vertebrae.

The nonmalignant changes produced in bone by heavy irradiation have never been adequately studied either in human subjects or laboratory animals.^{14, 28} Roentgenographically, patchy areas of bone rarefaction and condensation may be seen as a result of either radium poisoning or external irradiation.^{8, 13, 29} The corresponding histological changes have not been clearly defined, perhaps because of a lack of interest among pathologists and perhaps because the bone changes are not readily seen in microscopical preparations. "Radiation osteitis" with its associated rarefaction and spontaneous fractures^{8, 13, 29} may result more from damage to the internal structure of bone matrix and disturbances of mineralization than from direct resorption of bone trabeculae. However, the striking microscopical changes in the bones of our rats, reported here only as incidental findings, would suggest that the possibilities of the histological approach have not been exhausted.

Paralysis of the hind legs was a constant clinical feature in all but one of the rats bearing osteogenic sarcomas and was observed in one rat in which careful search revealed no tumor. The latter instance is not explained, but in all of the others the tumor was so situated that it could exert direct mechanical pressure on the spinal cord or nerve roots.

It is interesting that Thomas and Bruner,¹⁰ Sabin, Doan and Forkner¹⁶ and Rosenthal and Grace¹⁵ all described paralyses of the hind legs in some of their radium-poisoned animals in which no tumors were found at autopsy. Since nervous tissue is highly radioresistant, the paralyses were probably secondary to skeletal damage and not a result of direct radiation damage to the brain or spinal cord.

Thomas and Bruner¹⁰ injected 40 to 60 μ g. of radium chloride into each of 8 rats and the animals died without tumors 183 to 258 days after the first injection. In our experiments the first osteogenic sarcoma was found 253 days after feeding radium, a time interval corresponding almost exactly to the longest survival of Thomas and Bruner's rats. It is reasonable to assume that these workers would have observed osteogenic sarcomas if their doses of radium had been small enough to permit their animals to survive a little longer. A comparison of our results with theirs brings up another interesting point. Subcutaneous injection of radium in their hands resulted in an average retention of 25 per cent, and the total body content of radium in their animals at death ranged between 8 and 17 μ g. Our animals retained only about 2 μ g. If their experiment and ours may be considered comparable in other respects, one might conclude that the induction of osteogenic sarcoma by radioactive deposits in the bones of rats requires a time interval of about 8 months and cannot be greatly hastened, even though the amount of radioactivity in the bones be increased by a factor of 5 or more. Such an inference is not inconsistent with what is known of tumor induction by other forms of radiation. A suitable latent period must always elapse, regardless of the dose, before tumors appear. The same principle applies to chemical carcinogenesis, for here, as well, increasing the dose of the carcinogenic agent will not shorten the latent period for tumor induction beyond a fixed minimum.³⁰ One might speculate on the bearing of this latent period on the mechanism of tumor induction. If the action of the tumor-inducing agent were simple and immediate, acting directly, let us say, to produce atypical mitoses or mutations in exposed cells as suggested by Henshaw,³¹ and others, we would expect greater doses to exert a greater effect and by the rules of probability result in the earlier appearance of a tumor. On the other hand, if the agent merely produces a specific type of damage and the neoplasm arises indirectly at some stage in the process of repair, then the minimum latent period might be determined by the rate of evolution of the repair process irrespective of the magnitude of the initial injury. It is difficult to determine the exact origin of the sarcomas in our rats. The new formation of bone in the vertebrae appeared to be a reparative rather than a neoplastic reaction since it was most promi-

nent in the regions of greatest bone damage and since the spicules of new bone were so oriented as to lend support to regions weakened by necrosis. However, Martland¹³ believed that "radiation osteitis" is potentially a malignant lesion and the process as seen in rats could readily serve as the starting point for the growth of a malignant bone-forming tumor.

SUMMARY AND CONCLUSIONS

Osteogenic sarcomas appeared in the vertebrae or pelvic bones in 9 of 13 male Wistar rats after feeding each animal 100 μ g. of radium. Within 10 days after feeding, the animals had excreted 95 per cent of the radium and the average amount retained at the end of 10 months was only 2 μ g. The induction time from the first radium feeding to the discovery of the tumors was 253 to 426 days and averaged 365 days. Two of the nine primary tumors metastasized, one to the pelvic lymph nodes and one to the spleen. Three of the tumors were successfully transplanted to other rats. One has been maintained through 7 serial generations. The high phosphatase level present in the original tumors has been maintained in subsequent transplants.

The bone marrow of all of the rats was hypoplastic and showed generalized immaturity and abnormal deposits of hemosiderin. Extensive hemosiderosis was present in the spleens together with slight atrophy and extramedullary hematopoiesis. Widespread necrosis of bone was present in all of the rats and atypical new bone formation was found in all but one. Partially frustrated attempts to regenerate bone in regions of radium necrosis may be responsible for the ultimate appearance of osteogenic sarcomas.

In conclusion, the osteogenic sarcomas and other pathological changes consequent to radium poisoning in human beings have been reproduced in rats with a fair degree of fidelity and a readily transplantable osteogenic sarcoma of rats has been obtained.

Assays for alkaline phosphatase activity were conducted by Miss Dorothy M. Tibbetts. Dr. Austin M. Brues explanted fragments of two tumors in tissue culture.

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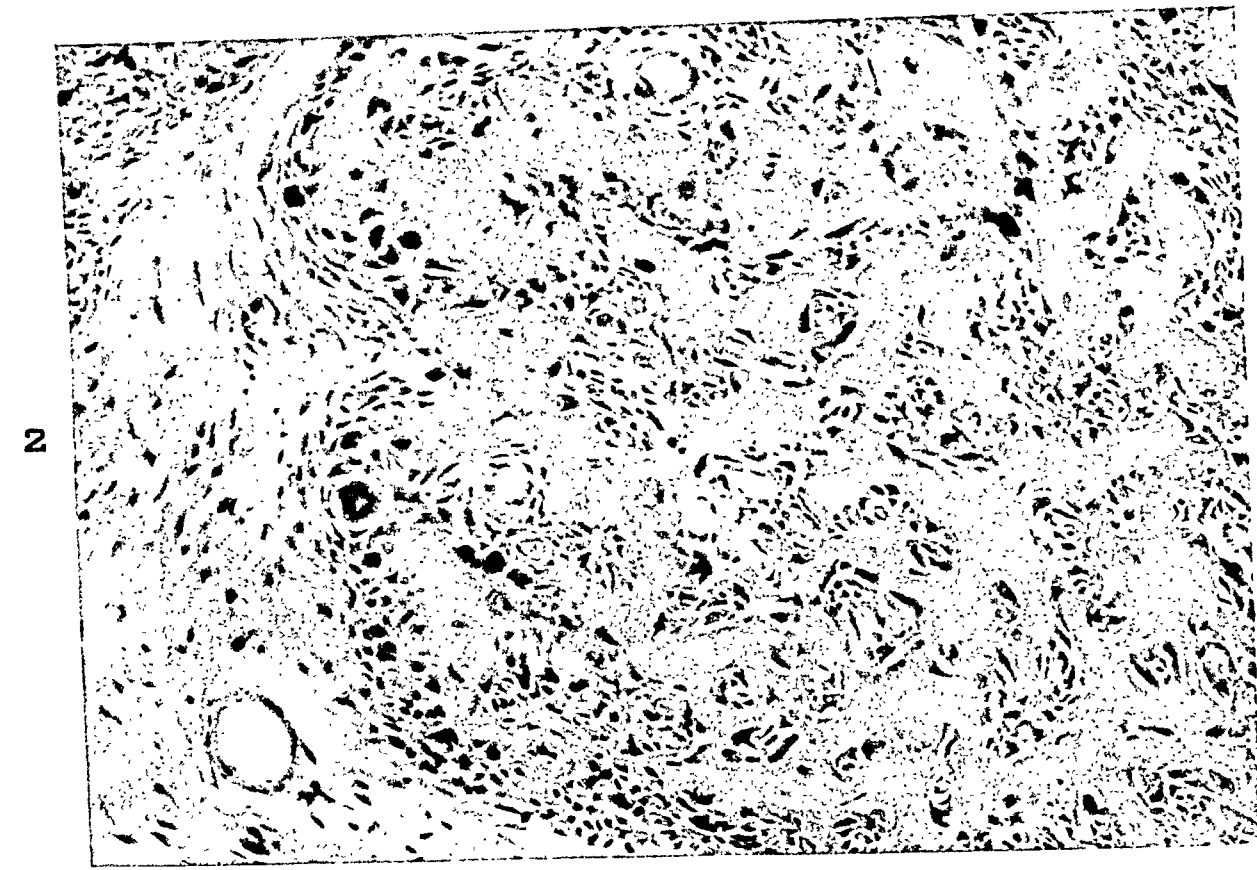
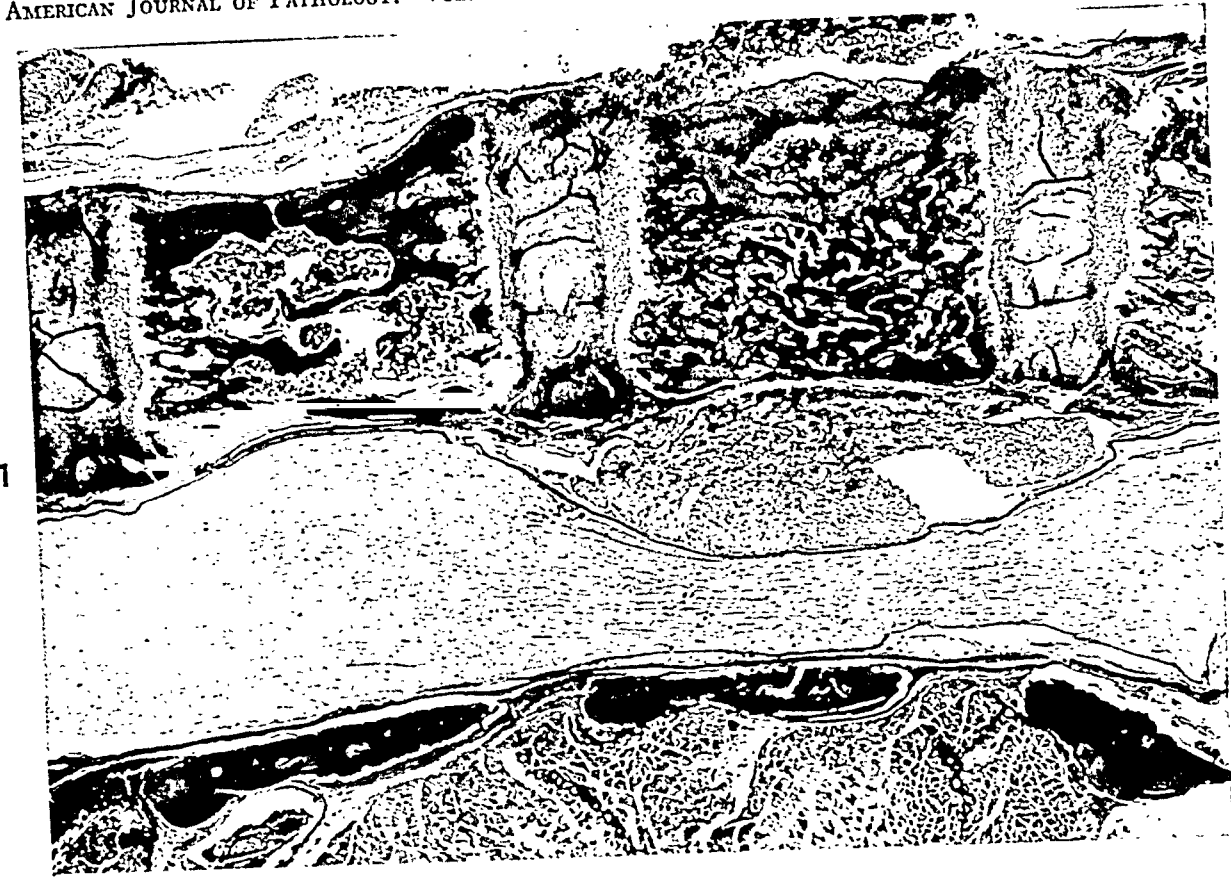
[Illustrations follow]

DESCRIPTION OF PLATES

PLATE I

FIG. 1. Radium rat 25635. Primary osteogenic sarcoma of second thoracic vertebra. The tumor has grown by expansion and has compressed the spinal cord without invading the dura. Bone changes are present in the corresponding vertebral body. $\times 13$.

FIG. 2. Radium rat 25641. Primary osteogenic sarcoma. $\times 235$.



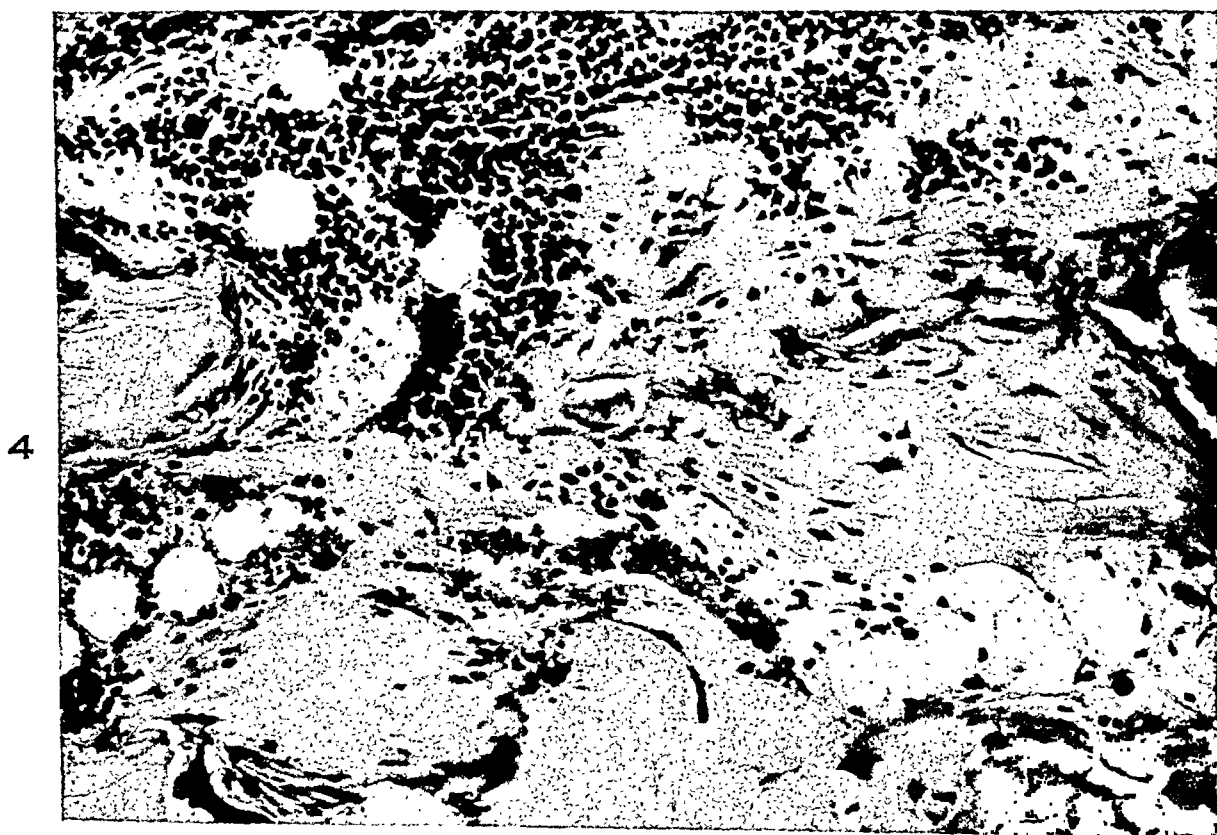
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PLATE 2

FIG. 3. Radium rat 25634. Periosteal new bone formation overlying area of bone necrosis in the cortex of a vertebral body. $\times 190$.

FIG. 4. Radium rat 25634. Atypical new bone formation in the marrow cavity of a vertebral body. $\times 225$.



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PLATE 3

FIG. 5. Radium rat 25630. Vertebral body showing peripheral atrophy of marrow and necrosis of cortical bone. $\times 21$.

FIG. 6. Radium rat 25631. Alkaline phosphatase stain of tumor invading striated muscle. The distribution of alkaline phosphatase is indicated by the areas which are stained black. It is confined rather sharply to the tumor. $\times 70$.

5



6



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ADAMANTOBLASTOMAS IN THE SLYE STOCK OF MICE *

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Previously, all studies dealing with the "adamantinomas" have depended upon material removed for biopsy, surgical specimens and post-mortem findings, chiefly from human subjects. While a great deal of information was obtained in this way, certain limitations were apparent. Among these was the fact that the site of origin disappeared either through obliteration by the growth, natural inclusion into the tumor, or by other means such as damage during surgical intervention.

Animals, and more specifically rodents, constitute a better source of material because the entire head can be sectioned and studied, thus retaining all original relationships.

Wells,¹ in his Trimble lecture, stated that:

"There is no fundamental difference between the tumors which occur in man and those which occur in animals. . . . Cancer in mice appears in most of the forms seen in man, and in far greater variety than had previously been supposed. The importance of the demonstration of this abundant variety of tumors in mice lies in the fact that it establishes the identity of neoplastic disease of mice with that in man. Nearly all the tumors that are found behave in much the same way, occur at a corresponding period of life, in response to similar conditions, and present exactly the same histological structure as similar tumors in man."

Thus, because of the nature of the material as well as the number of animals available, I considered myself very fortunate in obtaining for this study a group of mice with epithelial tumors of the jaw. Many interesting aspects of the tumor problem presented themselves. However, I limited my efforts to a classification of central epithelial tumors of the jaw based on morphology and histology, and primarily to a search for the origin of these tumors.

SYNONYMS AND DEFINITION

"Adamantinomas" are referred to in the literature by various names. Among these are adamantinoma, adamantoma, ameloblastoma, enameloblastoma, cystadenoma adamantinum, epithelioma adamantinum, adamantinocarcinoma, adamantoblastoma, adenocarcinoma, cystosarcoma, multilocular cysts and, in some instances, follicular cysts or den-

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tigerous cysts. The more common of these names are: adamantinoma, ameloblastoma and adamantoblastoma.

Malassez,² in 1885, coined the term "adamantine epithelioma" to designate these tumors as epithelial in character and derived from enamel-forming tissue. In 1902, Borst³ introduced the more generally accepted term "adamantinoma."

Adamantinoma and adamantoma are derived from the Greek ἀδάμας meaning "of the hardness of stone." In 1910, Galippe⁴ maintained that the term "adamantinoma" signified a growth composed of formed enamel, *i.e.*, a tumor of adamantine structure. However, Kronfeld⁵ pointed out that pure adamantinomas never contain enamel. The term "adamantinoma," therefore, meaning a tumor composed of and limited to adamantine structure, must be a misnomer since cells and structures other than those adamantine in form are often found.

Enameloblastoma signifies a tumor of enameloblasts, *i.e.*, already specialized enamel-forming cells. Although enameloblasts or cells simulating their features are sometimes observed, it is by no means the typical cell in all such tumors. This term should be discarded.

Ivy and Churchill⁶ were the first to apply the name "ameloblastoma" to this group of tumors. Robinson,⁷ in his review of 379 cases, has subscribed to its use saying that it is the most descriptive. He defined it as a tumor arising from the odontogenic apparatus, or from cells with a potentiality for forming tissues of the enamel organ.

Ameloblastoma, etymologically, means a tumor from or of enamel-forming cells. More precisely, it tends to convey the idea that the ameloblastic stage of development or the embryonal enamel-forming cell is the typical basic cell in all instances. This is not generally true.

The adamantocarcinoma or adamantinocarcinoma is defined as a malignant epithelial tumor of adamantine structure. Such cases have been reported in the literature. In this study, I have observed a group with definite carcinomatous characteristics but, since it comprised only a fraction of all the cases, I believe that the term adamantocarcinoma should be reserved as a subheading.

Epithelioma adamantinum is another term advocated to differentiate the malignant from the more benign "adamantinomas." This is a needless differentiation and, if used, should be a subdivision.

Multilocular cysts, follicular cysts and dentigerous cysts are purely descriptive terms from a morphologic standpoint. They do not convey information concerning origin or histologic structure. These terms simply tell us whether the tumor is unilocular or multilocular in structure and, if unilocular, whether or not a tooth is included in the growth.

Since all these terms are lacking in some particular, a more suitable

term is desirable. This name should include information concerning the principal cells of origin, with histologic and morphologic descriptive adjectives. Such a name, first suggested, to my knowledge, by Thoma,⁸ is adamantoblastoma. Adamantoblastoma is the generic term which I accept and which I will use when referring to this group of tumors.

My definition of adamantoblastoma is a tumor which arises from the embryonal epithelial cells of the enamel organ. The unspecialized epithelial cells of the enamel organ are capable of forming any or all of a large variety of epithelial cell forms through their embryonic multipotentiality. The term adamantoblastoma is not limited in application to growths of any particular form of epithelial cell nor to any particular stage of cellular development, but rather includes all types which may be derived from the embryonic epithelial cells of the enamel organ. This definition is based on conclusions from the material which is to follow.

LITERATURE WITH REFERENCE TO ORIGIN

Broca,⁹ in 1868, reported his observations upon the adamantoblastoma, although cystic tumors were already recorded in the literature at that time. Falkson,¹⁰ in 1879, gave the first complete description of an adamantoblastoma. Since then, many opinions have been expressed as to the origin, malignancy and general nature of these growths.

From a clinical standpoint, interest in these tumors centers mainly about their possible malignancy. However, if the site of their origin could be determined, the problem of malignancy might be better explained. In the literature are found reports of many studies dealing with the search for the origin of adamantoblastomas and yielding a number of theories, all materially different. Thus, the adamantoblastoma was thought to be derived from:

- (1) residual epithelial cell nests from (a) enamel organ, (b) Hertwig's sheath, or (c) dental lamina
- (2) proliferative disturbance of the enamel organ or the tissue forming it
- (3) mucous membrane epithelium of the jaw
- (4) the epithelium of odontogenic cysts

The origin of adamantoblastomas occurring in remote structures such as the brain or tibia must also be considered in the light of independent growths.

Epithelial Cell Nests. Malassez,² in 1885, was the first to observe epithelial cells in the peridental membrane about the roots of teeth. These he called paradental epithelial débris, which, he continued, might become proliferative and give rise to epithelial growths in the

jaws, including "adamantinomas." This idea has been widely accepted; however, without positive evidence.

It is generally agreed that the remnants of the sheath of Hertwig and the dental lamina are the chief sources of these epithelial cell rests. Of greater importance is the origin of the Hertwig's sheath, which is still in dispute. Some state that it is derived from the outer multipotential epithelial cells of the enamel organ or from the inner specialized ameloblastic layer, or, from both. Orban¹¹ stated that it is formed from both. Diamond¹² maintained that it is derived from the outer cells of the enamel organ.

Epithelial cell nests are believed to be very common in the jaws. They may be found in the dental follicle before the tooth has erupted, in the adult periodontal membrane, and may occur in the marrow spaces adjoining dental crypts. Thoma⁸ and Kotanyi¹³ reported two cases of small adamantoblastomas in girls which developed between the teeth in lower jaws and presumably arose from epithelial rests in the periodontal membrane. Bauer¹⁴ associated the adamantoblastoma with an excess of tooth germs as well as epithelial débris. Cysts, he stated, may develop by overgrowth of epithelial columns through degenerative processes within the epithelial strands. The uppermost epithelial débris is often connected with oral epithelium and so keeps the potential capacity to differentiate into varieties of cells.

Ewing,¹⁵ in his book "Neoplastic Diseases," stated that the tumors of the "adamantinoma" group arise from paradental epithelial débris. Stout,¹⁶ in his text "Human Cancer," wrote that, since the cysts and tumors that form in the jaws are inside the bone and in no demonstrable way connected with the alveolar epithelium in the early stages of their evolution, the presumption would be very strong that they arise from epithelial débris.

Hankey,¹⁷ Masciottra,¹⁸ Hayes¹⁹ and Steensland²⁰ were of the opinion that adamantoblastomas arise from paradental epithelial rests. Murphy²¹ cited statistics showing that the development of these tumors is not in relation with the development of the teeth and is thus opposed to the enamel organ theory and in harmony with that of aberrant epithelial rests. Krompecher,²² in his report of 5 cases, thought that such tumors arose from paradental débris or embryonal rests but added that they could also arise from the oral mucosa. McFarland and Patterson,²³ after a critical review of 196 cases, reported in the medical and dental literature, concluded that adamantoblastomas arise in the jaws from the paradental epithelial débris.

In contradistinction, James and Counsell,²⁴ two prominent British investigators, stated that there is no reason to believe that the epi-

thelial rests play any part in the production of pathologic epithelium. Hatton ²⁵ also said that there is little reason to consider that Malassez' epithelial débris has anything to do with the genesis of adamantoblastoma. The views of these latter authors will be cited again.

Enamel Organ. The enamel organ is often cited in the literature as the origin of adamantoblastomas. This designation is vague since this organ is composed of several strata, any or all of which may be considered the origin. It is composed of an inner layer of ameloblasts, the stratum intermedium and stellate reticulum, in that order, and an outer layer composed of embryonal epithelial cells. Few of the authors who consider the enamel organ the origin of adamantoblastomas state definitely which are the responsible layers. Broca,⁹ Falkson¹⁰ and Hatton ²⁵ point to the enamel organ as the site of origin, each believing that these tumors arise from overgrowths of the dental germ, supernumerary tooth buds and dental lamina or tooth bud respectively.

Gentsch ²⁶ maintained that true adamantinomas occur only in the jaws, since they arise from the enamel organ of developing teeth. Geschickter ²⁷ observed adamantoblastomas in negro patients, many of whom had rickets. He concluded that this deficiency might have caused some disturbance in the enamel organ which went on to tumor formation. Kegel,²⁸ who studied histories of surgical cases from the Johns Hopkins pathological laboratory, came to the conclusion that adamantoblastomas arise from the cells of the enamel organ rather than from the paradental débris of Malassez. He regarded the inner epithelial layer as the origin rather than the outer and upper layers. The latter, he stated, give rise to the so-called epithelial débris.

Colyer and Sprawson,²⁹ on the other hand, believed that the adamantoblastoma does not originate from the enamel organ.

Mucous Membrane. The epithelial cells of mucous membranes have been considered a possible site of origin of adamantoblastomas. Colyer and Sprawson,²⁹ Büchtemann,³⁰ Eve,³¹ von Bakay,³² Kuru,³³ Kaufmann ³⁴ and Gullifer ³⁵ subscribed to this theory. Several of these investigators reported cases showing proliferations attached to the oral epithelium. Robinson ³⁶ reported a case of peripheral adamantoblastoma composed of squamous, glandular and enamel-organ epithelium. This tumor developed on the lingual side of the ramus of the mandible but did not involve the underlying bone; hence the inference is that its origin was in the oral epithelium.

Odontogenic Cysts. That adamantoblastomas may arise from odontogenic cysts is another view held by some investigators. Churchill ³⁷ described two cases in which dentigerous cysts of the jaws seemed to assume ameloblastomatous characters. Schroff ³⁸ observed a case which

"consisted of a dilated cyst membrane that microscopically showed the structure of a follicular cyst. . . . A short distance from the cyst was a solid mass, which microscopically showed the structure of an adamantinoma." Cahn,³⁹ in a case report of a dentigerous cyst, observed mural swellings on the inner surface of the sac which, he contended, possessed the potentiality of developing into an adamantoblastoma. Hankey¹⁷ described a multilocular cyst arising from a maxillary dental cyst. Kotanyi⁴⁰ believed that dental cystic membranes should be removed in their entirety to prevent them from giving rise to potential cancerous masses. During the healing process following removal of a follicular cyst by the partial Partsch method, Becker⁴¹ observed epithelial sprouts, which upon histologic examination were of adamantoblastic character, in the pavement epithelium of the retained cyst sac. Wigdortschik⁴² reported a case in which a cyst of the mandible was treated by the Partsch method and recurred a year later in the form of an adamantoblastoma. Morlet and Morlet⁴³ described a tumor in the lower jaw which presented all the intermediate stages between a cyst and adamantinoma. This case, they maintained, confirms the common origin of the two affections.

Remote Structures. Until 1892 it was quite generally accepted that the adamantinoma was to be found only in the jaws. Onanoff⁴⁴ at this time observed that certain epithelial pituitary gland tumors exhibited marked similarities to the adamantoblastoma of the jaw. Since then, many such tumors have been reported and it is now quite commonly agreed that they also fall into the category of adamantoblastomas. These occur also in the posterior wall of the pharynx in the region where the hypophyseal duct develops. They are often referred to as hypophyseal duct tumors or craniopharyngiomas.

According to Duffy,⁴⁵ the pituitary duct, which forms from the ectoderm of the oral cavity, gives rise to epidermal cell rests from which adamantinomas may arise. He distinguished these tumors from the cysts of Rathke's pouch which develop from the cleft between the anterior and posterior lobes and which are lined by ciliated epithelium. Duffy described two cases, one of an intracystic squamous epithelial papilloma arising from a rest of the hypophyseal duct in the anterior lobe and a second of a cystic suprasellar tumor with adamantinomatous characteristics developing from an infundibular squamous epithelial rest of the hypophyseal duct. McFarland and Patterson,²³ in their review of the literature, also concluded that adamantinomas in the hypophysis arise from squamous epithelial debris of the hypophyseal duct. Twenty-six cases of adamantinoma of the pituitary gland, two cases of adamantinoma in the tibia and one in the upper lip were re-

ported in this review. Drummond⁴⁶ described a case of infrasellar adamantinoma which developed from isolated paradental debris found along the floor of the sella turcica. It eventually grew by way of the sphenoidal septum into the vomer.

Wohl⁴⁷ described a very hard tumor in the upper lip not connected to the jaw which, on microscopic examination, presented the typical features of adamantinoma. (This case is included in the review by McFarland and Patterson.²³)

Fischer⁴⁸ and Baker and Hawksley⁴⁹ reported adamantinomas in the tibia. Both were believed to be primary. Wolfort and Sloane,⁵⁰ in their report of two cases of adamantinoma in the tibia, concluded that a fragment of epidermis must have been included in an embryonic malformation and that it was excited to proliferation.

Robinson,⁷ in a review of 379 cases of ameloblastomas, found 7 cases of growths in the tibia. On the basis of his comprehensive study and in view of the current inadequate knowledge of the dento-cystic tumors, he concluded that etiologic considerations are, at best, founded only on theoretical grounds. In his opinion the adamantoblastomas arise from some part of the odontogenic apparatus or from cells with a potentiality for development into tooth-forming tissues.

LITERATURE WITH REFERENCE TO MALIGNANCY

One other feature of adamantoblastoma pertinent to this study is the question of malignancy. Some authors maintain that these growths are benign; others believe that they are benign but potentially malignant and still others are of the opinion that they are only locally malignant.

Bauer,¹⁴ basing his opinion on microscopic findings, maintained that cystic adamantoblastomas are benign tumors. He considered the reported cases of metastases as doubtful. Robinson,⁷ in his review of 379 cases, cited 17 in which evidences of malignancy were found. In 9, metastases were observed. In 119, recurrences were reported following removal. In many, the recurrence was traced to incomplete enucleation. He concluded that adamantoblastomas are benign and that the relatively small number with malignancy are atypical.

Lemaitre, Delater and Ardoin⁵¹ considered adamantoblastomas to be locally malignant tumors because they possess the power of invasion into the surrounding tissues and are distinguished from the highly malignant neoplasms by the fact that they grow slowly and rarely show mitotic figures. In rare instances, these authors found that adamantoblastomas changed into frankly malignant neoplasms. They cited the case of a boy of 17 years in whom an adamantoblastoma recurred fol-

lowing its removal. The adamantine type of celi had changed into a form exactly resembling the squamous epidermal type with intercellular bridges. Masciottra¹⁸ cited three instances of recurrences. Logsdon⁵² stated that recurrence is common if the tumor is incompletely removed. Moore⁵³ described a case of a man, 38 years of age, who had eight recurrences in the mandible in 7 years. Finally, the jaw was resected. At the last appearance a recurrence was observed in the stump. Frantz and Stix⁵⁴ reported several recurrences of an adamantoblastoma over a period of 51 years.

Ghosh⁵⁵ described the case of a boy, 18 years old, in whom a partly solid and partly cystic adamantoblastoma invaded the antrum. Broders and MacCarty⁵⁶ believed that, histologically, the adamantoblastoma closely simulates the squamous cell carcinoma. Oinoue⁵⁷ presented a case of adamantoblastoma primary in the mandible which metastasized to the lung, causing the death of the patient. Vorzimer and Perla⁵⁸ also had a case which metastasized to the lung but here they considered the possibility of aspiration during operation. Ewing¹⁵ reported two cases with metastases. In one, small metastases were found in the lung and cervical lymph nodes, and in the other a fourth recurrence was in the cervical nodes and loose tissues of the neck.

Dorrance⁵⁹ emphasized the potential malignancy of adamantoblastoma. Spring⁶⁰ stated that recurrences are frequent in adamantoblastoma and that these tumors are known to develop the histologic characteristics of carcinoma. Geschickter²⁷ looked upon adamantoblastomas as neoplastic and potentially malignant homologues of follicular cysts.

Hatton²⁵ considered the solid adamantoblastoma as malignant. He stated that the multilocular cysts are equally malignant since they both tend to infiltrate and recur after excision. Sprawson and Keizer⁶¹ contended that the adamantoblastoma should be designated as basal cell carcinoma on the basis of histologic study and malignant properties. Dew and Miller⁶² maintained that these tumors possess the aggressive properties of epitheliomas of local malignancy.

Simmons,⁶³ in his report of 12 cases of adamantoblastoma, maintained that, although it is usually true that these tumors are benign, they are potentially malignant. He cited 2 cases with glandular metastases. These metastases occurred late, were regional at first and, in 1 case in which they were later general, dissemination was not demonstrated until 14 years after the onset of the disease. In the second case metastases in the glands of the neck appeared 12 years after the original tumor. Sections of the primary tumor and the metastatic glands confirmed the primary-secondary relationship. Conservative

operations were performed in 10 cases and in each instance there was a recurrence. Two patients died from local extension of the disease and sepsis and 1 of metastasis.

From this summary of the literature it will be seen that adamantoblastomas are classified as benign tumors by many writers. The majority, however, believe that they should be grouped with the neoplasms of local malignancy, since they invade and destroy the surrounding bone and soft tissues and, when handled conservatively by surgical means alone, they often recur. Moreover, there is general agreement that these tumors possess the property of potential malignancy. The classification of frank malignancy is reserved for those rare adamantoblastomas which have demonstrated their potential malignancy by metastasizing to neighboring lymph nodes, soft tissues of the neck, lungs, or other structures.

EMBRYOLOGY, HISTOLOGY AND ANATOMY OF THE RODENT INCISOR

Since this study is based upon incisor teeth of mice and is concerned particularly with the formative enamel organ, review of the normal embryology, histology and anatomy is essential.

The incisor teeth of rodents are continuously growing and erupting structures, but in their functional capacity they wear away so that the teeth in normal adults remain of constant size. The rate of wear, then, equals the rate of eruption and formation. The failure of an incisor to occlude normally with its antagonist results in an elongation unchecked by wearing. The normal rate of eruption is about 2 mm. for the upper and 2.8 mm. for the lower teeth per week. The teeth renew themselves completely every 35 to 45 days. These teeth grow by apposition of dentin at the pulpal surface and by elongation of the basal part where is found a widely open apical foramen. The dentin comprises the bulk of the tooth. The enamel is formed only on the labial or convex side of the tooth and overlaps slightly the lateral surfaces. The remaining part of the tooth is covered with cementum.

Enamel is not formed over the tip of the tooth at any time. Before eruption this area is filled with so-called "osteodentin" produced by the underlying pulp cells. As the tip wears away with use, the pulp forms more of this substance, which has been called secondary dentin, so that the pulp is never exposed.

The dentinal papilla, composed of dentinoblasts, is situated at the posterior end of the developing and erupting incisor. These dentinoblasts are the first cells to differentiate, laying down dentin shortly before the enamel organ becomes functional to produce enamel. External and inferior to the dentinal papilla lies the basal end of the

formative enamel organ. Here, a mass of closely packed embryonic epithelial cells give rise to its cellular structures. These cells are functional throughout the life of the animal in accordance with the persistent growth of these teeth, *i.e.*, the organ is not transitory as in man.

The enamel organ has fundamentally the same four layers as seen in man. The inner layer consists of distinct tall columnar ameloblasts, a stratum intermedium of two or three layers of flattened cells and a stellate reticulum of loosely arranged cells. The outer layer consists of a single row of cuboidal cells which sends out papilla-like buds into the connective tissue. Numerous blood vessels of the latter occupy the depressions between the epithelial elevations. Toward the middle portion of the labial surface, the enamel organ reaches its highest functional development, the ameloblasts are tallest and the stratum intermedium consists of one or two rows of cuboidal cells. The stellate reticulum loses its characteristic appearance and seems to be replaced by the outer enamel epithelium, which is now in contact with the stratum intermedium. The papillae thus formed are more prominent and considerably higher than at the basal end, and are surrounded by an abundant capillary blood supply.

As the tooth erupts, the ameloblasts move forward at an equal rate and recede labially with the apposition of organic enamel matrix.¹² Enamel formation starts at the basal end and increases in thickness, becoming more fully calcified as it extends anteriorly. In the rat the normal daily rate of enamel formation is $16\ \mu$.

A very thin layer of cementum covers the lingual, mesial and distal surfaces, gradually increasing to a thickness of 3 to $4\ \mu$ toward the incisal end. The peridental membrane is comparatively wide and has a rich blood supply.

As the enamel organ proceeds forward with the erupting tooth, regressive and degenerative changes occur in it. The ameloblasts gradually become shorter and cuboidal, losing their power of amelogenesis. The stratum intermedium and the external layer of epithelial cells also show regressive changes fusing with the degenerated ameloblasts. The resultant structure takes on the appearance of a flattened stratified squamous epithelium, joining with the squamous cells of the gingivae at the oral junction.

Functionally, the rodent and human enamel organs serve the same purpose, formation of enamel. The only important difference revolves about the property of the rodent incisor of continuously growing and erupting, as differentiated from the human tooth which has a limited developmental stage. Whereas the basal enamel organ and formative dentin cells in the rodent incisor proliferate throughout life, in man, at

the completion of enamel formation and before eruption, the enamel organ degenerates. This functional difference in the two enamel organs is not as important as it may seem, since the onset of tumor formation in man must occur before degeneration of the enamel organ takes place in order to comply with the views already stated citing the enamel organ as the site of origin of adamantoblastomas. For this reason, as well as others already stated, the microscopic description of the origin of these growths in mice may, with equal reasonableness, be applied to man.

MATERIAL

The material for this study was a group of 79 mice (Table 1) obtained from the Maude Slye colony at the University of Chicago. Only animals were chosen in which tumors of the jaw were present. All growths were found in mice wherein heredity was the factor under study. I will not attempt in this paper to delve into the genetic problem involved. This has been admirably stated by Wells, Slye and Holmes.^{1, 64-69}

Efforts had been directed toward providing balanced diets and good hygienic conditions, and the mice were allowed to live their full life span.

METHODS

After natural death, the heads of these animals were removed and placed in a 4 per cent formaldehyde solution and allowed to remain there for periods varying from 3 months to 2 years before being acquired by me. My first procedure was to record gross descriptions; then, 25 heads were sawed anteroposteriorly in the midsagittal plane for the purpose of taking x-rays. By this method it was found that both halves could be radiographed more accurately. The remaining heads were radiographed intact. All radiographs were taken at 20 inch target-film distance, using 50 kv. and 10 ma. of current. Exposure time was 1.5 to 2.0 seconds. The heads were then decalcified in a 5 per cent nitric acid solution in which the diluent was 4 per cent formaldehyde. Daily changes of the solution were made until the ammonium oxalate test showed that the decalcification was complete, the average length of time being 72 hours.

The specimens were then washed in running water for 24 hours and dehydrated in the alcohols in the usual manner. They were then placed in 4 to 5 per cent celloidin and tightly sealed, where they were allowed to remain for an average of 4 months. The next change was to 10 per cent celloidin for 1 month and then to 14 per cent celloidin for another month. Finally, they were laid in small Stender staining dishes containing 14 per cent celloidin, allowing slow evaporation and concentration

TABLE I

*Seventy-nine Mice from Maude Slye Colony of University of Chicago
(Animals Arranged According to Findings)*

A. ADAMANTOBLASTOMAS		CONCOMITANT FINDINGS
I. MONOCYSTIC		(Findings in opposite side of mandible in same animal)
(a) Monolobulated		
	2	Multicystic
	5	Monocystic
	6	Normal
	7	Normal
	8	Monocystic
	12	Multicystic solid
	13	Multicystic epidermoid
	16	Multicystic epidermoid
	21	Sarco (giant cell)-adamantoblastoma
	30	Monocystic
	31	Monocystic
	32	Sarco (osteogenic)-adamantoblastoma
	33	Monocystic
	34	Monocystic
	36	Monocystic multilobulated
	37	Monocystic
	41	Monocystic
	42	Monocystic
	43	Multicystic solid
	44	Sarco-adamantoblastoma
	48	Monocystic
	49	Normal
	52	Normal
	55	Multicystic solid
	57	Multicystic epidermoid
	58	Multicystic epidermoid
	59	Multicystic epidermoid
	60	Multicystic epidermoid
	61	Monocystic
	62	Multicystic epidermoid
	63	Monocystic
	65	Multicystic epidermoid
	67	Multicystic solid
	68	Monocystic
	69	Multicystic
	70	Multicystic epidermoid
	71	Solid epidermoid
	72	Multicystic epidermoid
(b) Multilobulated		
	10	Normal
	15	Normal
	19	Multicystic epidermoid
	36	Monocystic
2. MULTICYSTIC		
(a) Without solid masses		
	2	Monocystic
	35	Multicystic
	39	Multicystic
	50	Multicystic solid
	54	Sarco (spindle cell)-adamantoblastoma
	64	Multicystic
	73	Monocystic
	74	Normal
	75	Normal
	76	Normal

TABLE I—*Continued*

(b) Multicystic solid

12	Monocystic
20	Multicystic solid
43	Monocystic
50	Multicystic
55	Monocystic
66	Multicystic solid
67	Monocystic

(c) Multicystic epidermoid

9	Normal
13	Monocystic
16	Monocystic
19	Monocystic multilobulated
38	Multicystic epidermoid
56	Normal
57	Monocystic
58	Monocystic
59	Monocystic
60	Monocystic
62	Monocystic
65	Monocystic
70	Monocystic
72	Monocystic
77	Normal

3. SOLID EPIDERMOID

40	Normal
51	Normal
71	Monocystic

B. SARCO-ADAMANTOBLASTOMAS

1. SARCO (OSTEOGENIC)-ADAMANTOBLASTOMA

4	Bilateral
32	Monocystic

2. SARCO (SPINDLE CELL)-ADAMANTOBLASTOMA

17	Bilateral
54	Multicystic

3. SARCO (GIANT CELL)-ADAMANTOBLASTOMA

21	Monocystic
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4. SARCO (FIBRO)-ADAMANTOBLASTOMA

44	Monocystic
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MISCELLANEOUS FINDINGS

Sarcoma

1	Giant cell
3	Fibro-
14	Spindle cell (in cheek)
18	Osteogenic—odontoma
22	Osteogenic (in both mandible and maxilla)
45	Osteogenic
65	Round cell
78	Osteogenic
69	Osteofibroma

Odontoma

11	Odontoma
18	Sarco (osteogenic)-odontoma

Others

46	Multiple abscesses of tongue and jaws
47	Extra-mandibular growth
53	Ranula
79	Multiple abscesses

to take place. More celloidin was added as needed to cover the exposed tissue surfaces. The specimens were then removed to chloroform desiccators for final hardening, and stored in 70 per cent alcohol until ready for sectioning.

Serial cross sections or longitudinal sections, 10 μ thick, were cut. Every tenth section was mounted and stained with a dilute solution of Harris' hematoxylin. Sections were allowed to remain in this solution overnight, after which they were counterstained with eosin. The intermediate sections were stored in 70 per cent alcohol and used only when needed.

Special stains were used in all cases where any doubt existed as to the correct diagnosis or where more accurate differentiation of tissues was desired. The most commonly used special stain was the Heidenhain's azan stain.

OBSERVATIONS

Gross Pathology

The heads of the animals were grossly distorted by the tumors, some of which were firm, others soft, while the usual finding of crepitation was a prominent feature in the larger growths. These expanded laterally to such an extent as to almost double the normal horizontal width of the face. Others protruded from the under surface of the mandible and greatly displaced the lower jaw. Still others involved both halves of the mandible while a few were bounded by the orbit superiorly, the external auditory meatus distally, the midline mesially and the lower border of the mandible inferiorly.

In all cases, the incisor teeth only were involved in the growths. In most of these, the incisors were forced out of their natural positions so that the resultant malocclusion prevented normal wear. Thus the teeth attained extreme lengths and varied shapes, protruding from or into the mouth abnormally.

In many instances these displaced teeth penetrated the cheeks, opposing jaws, tongue and nasal cavity, causing soft tissue abscesses and osteomyelitis. In several animals in which the tumor mass extended into the mouth, difficulty in eating resulted in inanition. In others, mastication caused surface abrasions which developed into ulcerations with secondary infection. In some cases, the infection eventually caused the death of the animal.

Roentgenographic Examination

Radiographs of the head of each animal were taken from two different angles before decalcification. Intra-oral dental films were used. The tumors presented a variety of appearances. Monocystic involve-

ment was most frequently observed (Fig. 2). Multicystic tumors, with thin radiopaque lines dividing the lobules, were next in order of frequency. Growths giving the homogeneous radiolucent appearance of soft tissue were also observed. The latter proved to be solid epithelial tumors.

The molar teeth were displaced by the expanded tumors. In the radiographs, crowns of the distorted incisor teeth were greatly elongated, and took on the form of concentric circles or sectional arcs (Fig. 1). The roots of a few were found to be shortened, but only in teeth involved in the growths. The normal structural outlines of the mandible on the side of the growth could not be seen because, as the growth expanded, the bone also expanded and thinned out or was lost entirely (Fig. 2). Portions of the growth extended into the ramus of the mandible, often obliterating it completely. Posteriorly the tumors were observed to extend distally to the ear (Fig. 1).

Microscopic Pathology

The adamantoblastomas of my series were found to arise in the mandible only. This does not exclude the maxilla as a possible site. These tumors were intra-osseous or central and extended over wide areas, causing great destruction and displacement of normal structures. The normal bony outlines of the affected mandibles were completely lost, especially in the more posterior regions where the maximum size of the tumor was most often found (Figs. 3, 4 and 6).

Displacement of the lower incisor teeth of the involved jaws was a common finding (Figs. 4 and 6). In most instances the entire tooth was bodily displaced from its normal position toward the midline and superiorly by the expansive force of the tumors. The growths in these animals were inferior to the teeth, below the enamel space (Figs. 7 and 8). Distortion of tooth contour by tumor pressure was observed quite frequently but the intrinsic structural development of the enamel, dentin and cementum was not disturbed (Fig. 4). The molar teeth of the involved jaws showed no abnormalities but that of change in position caused by tumor pressure. The base of the tongue was invaded by neoplastic tissue in several cases, and the tongue itself was grossly displaced (Fig. 42).

In one animal, epithelial strands from the main tumor mass invaded the root of an incisor tooth, proliferating widely in the pulp chamber and canal. This epithelial mass was seen to break down and form a fairly large cyst in the body of the tooth which, by its outward pressure, caused complete resorption of the dentin, enamel and cementum in the formative portions of the tooth.

Many animals showed invasion of the ramus with replacement of the mandible by neoplastic tissue (Figs. 4, 6 and 41). Resorption and regeneration of mandibular bone were observed in all involved jaws. Maintenance of some semblance of a bony periphery around the tumor masses was observed, but even this thin shell was often absent so that only a narrow layer of fibrous connective tissue and elongated muscle fibers formed the external limits of the cyst (Figs. 4 and 6). In some mandibles little or no normal bone marrow was found due to its resorption, while in others fibrous connective tissue or invading epithelial masses filled the marrow spaces.

The striated muscles of the jaws were found to be lengthened and degenerated. In a few instances, only small remnants remained to indicate their presence in these regions (Figs. 4 and 6).

In eight animals, because of the extent of the mandibular growths, traumatic injuries occurred resulting in infections and suppurations. Oral ulcerations were observed spreading into the central portion of the tumors. Secondary infections were also seen in isolated extra-oral areas of these adamantoblastomas.

For purposes of further description, I have divided the tumors according to their (1) cystic or (2) solid character, some being composed of cystic structures only, while others were solid, and still others, both cystic and solid in different areas.

Cystic Structure

The linings of most cysts were composed of stratified squamous cells varying from two to five cells in thickness (Figs. 5 and 6). The cells were of the usual squamous variety with intercellular bridges. In many instances, however, the cellular linings were greatly distended with consequent flattening, forming thin, dark lines (Fig. 9). In such cases they were stretched to double and triple their normal lengths and flattened to one-third to one-fourth of their normal thickness. The remaining portion of the cyst wall was composed of a layer of fibrous connective tissue consisting in some cases of thick collagen fibers, in others of thin fibers which were arranged parallel to the periphery. Where bone was seen external to the cyst wall, it was compact, showing evidences of resorption on its internal surface and new bone formation on its periphery.

The contents of the cysts varied, but this did not seem to differentiate one type of adamantoblastoma from another. The composition of the cystic contents included: clear cystic fluid, cholesterol, foam cells, desquamated epithelial cells, inflammatory cells (round, polymorphonuclear, and plasma cells), hemorrhagic material, hemosiderin granules,

and keratohyaline structures. The cystic cavity was often entirely filled with clear fluid having a finely granular texture. Frequently clear fluid formed the bulk of the contents with various amounts of the other constituents and with no particular specificity (Fig. 6). Cholesterol slits (Fig. 5) and foam cells were often observed but always constituted a minor proportion of the contents. Desquamated epithelial cells (Fig. 9), usually in small numbers, were found close to the cyst membrane. In some instances the cystic space was entirely or partially filled with inflammatory accumulations (Figs. 5 and 31). Hemorrhage was occasionally observed, with red blood cells clearly distinguishable, little degeneration being present. In others, hemorrhagic debris in the form of clumps and densely granular structures was present as were phagocytic cells with ingested hemosiderin granules (Figs. 4 and 41). Keratohyaline structures were seen only in certain of the tumors. In some of these, keratin completely filled the cyst while in others it was found in varying degrees of dissolution (Figs. 7 and 10).

The keratohyaline structures in my group occurred in the multicystic epidermoid adamantoblastomas.

Solid Epithelial Structure

The solid epithelial portions of these growths varied in quantity and in cell type. Dense, broad sheets of epithelium with strands, cords and columns of cells, frequently anastomosing and branching, permeated the stroma. Central breakdown of such epithelial extensions was commonly seen with the degenerative masses tending to form other cysts (Figs. 7, 10, 11, 12, 13 and 14).

In a given tumor, the majority of cells were of one distinct type, but it was common to find all degrees of differentiation. The variations ranged from undifferentiated epithelium to differentiated stratified squamous epithelium or specialized adult ameloblasts. Epithelial cells and structures observed included: stratified squamous cells, epithelial pearls, adenomatous structures, stellate cells, adamantine-like cells, basal cells, embryonal syncytium, sarcoma-like epithelial cells. The stratified squamous cell was the most frequently observed type (Fig. 11). Broad sheets of such cells often formed large portions of the solid areas of adamantoblastomas. Intercellular bridges were clearly distinguishable in most cases (Fig. 11). Anaplasia was minimal (Figs. 12 and 15). The nuclei were large, hyperchromatism was infrequent (Figs. 13 and 14) and mitotic figures were rare (Fig. 38). The cytoplasm was granular and abundant. The branching and anastomosing of these epithelial cells gave the general microscopic appearance of a squamous cell carcinoma (Figs. 32, 35, 36 and 37).

Many variations among the epithelial cells were noted in most of the tumors. In some instances these variations comprised considerable portions of the tumor mass. Epithelial pearls in the form of bulbous masses, with concentric arrangement, were observed. These structures presented all stages of keratinization in passing from the outer layers of cells toward the center. The peripheral layers of such pearls were of the prickle cell type; keratohyaline granules appeared in cells of the inner layers, with gradual transformation into structureless masses of keratin. The epithelial pearls presented varying sizes and shapes, some being huge with large amounts of keratin while others were quite small. Also seen were large pearls in various degrees of dissolution (Figs. 7 and 10).

Gland-like arrangements of cuboidal and columnar cells without positive secretory activity were seen as isolated masses completely surrounded by stratified squamous cells (Figs. 12 and 13). These adenoma-like structures were not completely differentiated as such but assumed irregular alveolar arrangements.

Cells of the enamel organ type made up portions of the epithelial structures of the adamantoblastomas. The stellate stage of epithelial development was often found (Fig. 12). These cells appeared in isolated regions in groups of varying size. Resemblance to the stellate reticulum was further emphasized by the cells forming a latticework arrangement because of the joining of cytoplasmic strands. The intervening spaces were clear and filled with a mucoid material.

The highest degree of differentiation of epithelial cells was attained by those cells which were adamantine or enameloblastic in form. These cells were of the tall columnar type with hyperchromatic nuclei, irregularly situated in the densely stained cytoplasm. Such areas were small and infrequent. Although the individual cells resembled enameloblasts, the groups did not follow the enamel organ pattern. In those instances where areas of "stellate reticulum" and "enameloblasts" were seen, it was noted that most of them were separated and in no way functionally related to each other. Although the enameloblastic stage of development was reached by isolated groups of cells, the enamel-forming function was definitely lacking. *No formed enamel was observed.*

Basal cell epithelium (Fig. 14) in strands and columns frequently constituted considerable portions of the solid epithelium. The cells contained little cytoplasm and were smaller than the squamous variety. The nuclei stained densely with hematoxylin. Masses of degenerated basal cells with small cysts were seen in isolated areas. No keratinization was observed.

Areas of embryonal epithelial syncytium were seen in a small number of tumors (Fig. 15). The cells were undifferentiated, cuboidal in form

and widely separated by a pale, blue-staining material, mucoid in appearance. Occasionally the cytoplasmic strands joined and presented a uniform appearance.

In several instances, epithelial cells in broad sheets arranged themselves in patterns simulating spindle cell sarcoma (Fig. 16). The cells were elongated, with small amounts of granular cytoplasm and large, hyperchromatic nuclei. Intercellular bridges were indistinct. Mitotic figures were frequent. These masses of cells widely infiltrated the neighboring regions and surrounded portions of the connective tissue stroma and isolated bone spicules in the process of resorption.

Stroma

The amount of matrix varied considerably in different tumors. Those which were largely cystic contained small amounts of stroma, while the solid and partially solid adamantoblastomas usually contained large quantities. The thin strips of dense fibrous tissue between the cyst wall and the periphery of the purely cystic growths were compressed and avascular, and were found both with and without bony septa.

Three types of stromas were observed, heterogeneously distributed. In the first, hyalinized collagenous bundles predominated; the second was composed mainly of cellular fibroblasts, and the third was mostly sarcomatous in nature. The bundles of hyalinized collagen were most often seen. These appeared as dense, eosin-stained masses with narrow fibrocytes flattened between them (Figs. 17 and 18). Isolated epithelial infiltrations in the form of nests and narrow strands were often found surrounded by this collagen. In some tumors, where the epithelial tissue was abundant, small islands of collagen were surrounded by strands of epithelium in lattice-like arrangement (Fig. 13).

The second type of stroma with large, prominent fibroblasts (Fig. 19) was well vascularized. Networks of newly formed capillaries coursed through this stroma resembling granulation tissue (Fig. 21). Fibrous connective tissue was minimal, with only short, thin strips separating the fibroblasts. This is an embryonal type of stroma.

The third main type of matrix—sarcomatous—was found in only a few instances (Fig. 20). However, whenever it did occur the problem arose as to whether these were true sarcomas with some epithelial proliferation or adamantoblastomas with a sarcomatous matrix caused by a pronounced desmoplastic property. This problem was emphasized because, in several instances, definite mixed tumors (sarco-adamantoblastomas) were found. The predominating features of this type of matrix were: (1) areas of elongated spindle cells evenly arranged and uniform in size, forming the bulk of the tumor; (2) scanty intercellular substance with the cells close together; (3) cross section of bundles

appearing as round cells; (4) matrices more dense and more widely invasive locally, but limited peripherally by epithelial borders. While these four features might with equal accuracy be utilized in describing a sarco-adamantoblastoma (Fig. 22), my principal means of differentiating these as adamantoblastomas with sarcomatous matrices was in the degree of anaplasia and in peripheral limitation. Other findings in the stroma were: bony trabeculae and septa, remnants of resorbing bone, osteoclasts, new bone formations, infective and suppurative processes and hemorrhagic material.

Lobules of a single cyst and the individual cysts themselves were often separated from each other by bony trabeculae (Figs. 6 and 9). The thin septal layers of bone appeared compressed and were surrounded by small amounts of fibrous connective tissue. These bony structures were composed of fused, parallel layers, staining with varying degrees of intensity with hematoxylin. Osteocytes were absent or only faintly visible. Scattered in the stroma of some tumors were spicules of bone, the remnants of resorbed bone. These densely stained structures appeared in different shapes and sizes surrounded by fibrous connective tissue. Osteoclasts, in Howship's lacunae, were often observed. These large multinucleated cells were seen in some areas where active resorption of bone was apparent (Fig. 13).

Bone regeneration was a prominent feature in most tumors. The new formations of cortical bone often comprised considerable areas of the stroma. Usually they were located external to the central region of the adamantoblastoma as if to form the peripheral boundary of the tumor (Figs. 4 and 17). The new bone marrow spaces were filled with a vascular fibrous connective tissue in most cases but in a number of instances epithelial invasions from the main tumor mass penetrated deeply into these outlying structures (Fig. 35).

Infective and suppurative processes were found frequently, invariably arising from oral ulcerations or external jaw injuries (Fig. 42). These secondary infections were made evident by masses of round cells and polymorphonuclear leukocytes which sometimes occupied considerable portions of the entire tumor. The true picture of the tumor was often disturbed by the suppurative process which caused widespread liquefaction and necrosis. Recent and older hemorrhages were seen, with hemorrhagic debris and hemosiderin in the cytoplasm of large phagocytes (Fig. 21).

Vascularity

There was marked variation in the vascularity of these tumors. In the densely fibrous and hyalinized stroma, vascularity was minimal (Fig. 18). Although narrow, flattened blood vessels were observed be-

tween the bundles of collagen, they were few in number. The young fibroblastic matrix contained rich networks of capillaries and lymph channels. The structural endothelial cells were large and young in appearance. Numerous capillary anastomoses were observed coursing through the collagen-free stroma. Several tumors were observed which were rich in vascular channels. These were considerably oversized and close together, with little stromal material between them. The similarity to hemangiomas was striking but since these areas were purely local, occupying comparatively small portions of the main tumor mass, they were considered regions of atypical vascularization (Fig. 21).

Origin

The chief theories as to the origin of adamantoblastomas are three in number: (1) epithelial rests of Malassez; (2) mucous membrane of the mouth; (3) enamel organ. Of these, that of epithelial rests is the most favored. However, of 97 adamantoblastomas, only 5 cases, or about 5 per cent, were observed with epithelial rests in the peridental membrane, while of 30 normal mice, 2, or about 6 per cent, had epithelial rests in the peridental membrane. (Fifteen others were either mutilated for biopsy or had other tumors.) The epithelial rests were all inactive and purely local in character. In no instance was evidence of proliferation from epithelial rests seen. Except for a few tumors which completely encircled the incisor teeth, all were found on the *convex* side of the tooth far removed from the epithelial debris in the peridental membrane which covers the *concave* surface of the tooth (Figs. 23 and 24).

The next most popular theory attributes the origin to the enamel organ (Fig. 25). However, it has already been pointed out earlier in this paper that where the enamel organ is cited as the point of origin, the usual reference to it is vague in that it is considered in its entirety rather than as to any one of its four component layers. *In this study it was found that the enamel organ is unquestionably the site of origin of most of these adamantoblastomas and probably in all of them* (Figs. 23, 26, 27, 28, 29, 30, 31 and 32). Thus, of 97 adamantoblastomas, 87 showed unquestionable enamel organ origin with no other source seen. In 8, downgrowths of epithelium along the sides of oral ulcerations appeared to supply part of the tumor masses with what might be considered another site of origin. The remaining 2 were mutilated in obtaining material for biopsy.

In considering the particular stratum of the enamel organ which might be responsible for the origin of these tumors, I wish to point out especially the outer layer of epithelial cells (Fig. 25). These cells are

embryonal and unspecialized, retaining multipotential properties characteristic of embryonic epithelium. Proliferations of these outer cells of the enamel organ did occur, and were seen to form dense massive accumulations of epithelial cells external to the enamel space (Figs. 7, 8, 26, 27 and 29). The cells were small and their nuclei hyperchromatic, resembling at times a basal cell carcinoma. These proliferative masses retained their attachment to this outer layer. In some cases, the attachments were as thin as 0.1 mm. in width, and in others as wide as 6 mm. (Figs. 28 and 29). Several tumors presented interrupted attachments (Figs. 29 and 30). In most tumors, the attachments were found somewhere along the anterior half of the unerupted portion of the incisor tooth, with the main tumor mass posteriorly and below (Figs. 7 and 8). In the others the attachments were posteriorly, or anteriorly as far as the enamel organ-gingival junction. The width of the attachments from mesial to distal varied from one quarter to all of the convex-shaped enamel organ (Figs. 28 and 29). *Thus, the unspecialized epithelial cells forming the external layer of the enamel organ were determined to be the primary origin of all adamantoblastomas in this series (Fig. 32).*

The rôle of the gingivae and oral mucous membrane as points of origin was also considered. In no instance was there seen proliferation and downgrowth of the gingivae, except in the eight cases of oral ulcerations already cited. Even in those cases in which the site of attachment of the tumor was far enough anterior to be in contact with the oral gingivae, the identity of the attachment to the enamel organ was clearly retained. However, where oral ulcerations occurred, the growths appeared contiguous to the oral epithelium. Thus, it may be considered as a possible point of origin, but since the attachment to the enamel organ was also observed in all these tumors, the oral mucous membrane should be considered as a secondary site of origin.

Malignancy

In considering malignancy, I was guided by the criteria laid down by Ewing.¹⁵ These are:

1. The presence of metastatic lesions in the neighboring lymph nodes
2. Invasions and infiltrations into the surrounding regions
3. Local destructive properties
4. Local interference with function

Metastases. Metastases from the primary growth in the mandible to the submaxillary lymph nodes were observed in but two animals (heads only available) (Figs. 33 and 34). The parent tumor of one was a

multicystic, solid adamantoblastoma with carcinomatous features and the other was a multicystic epidermoid type of adamantoblastoma. The involved lymph nodes were markedly enlarged; mostly filled by the metastases, and the remaining lymphoid tissue appeared compressed. In general histologic features the metastases were reproductions of the parent tumors. The cells were small, with round, hyperchromatic and densely stained nuclei and little cytoplasm. Intercellular bridges were few, difficult to identify, and were observed in small isolated areas only.

Invasion. Infiltration of surrounding tissues was frequently observed in the types of adamantoblastoma which contained solid epithelial portions. Long strands from the epithelial masses infiltrated the bone marrow spaces, obliterating the normal structure (Figs. 35 and 36). These were seen to anastomose and branch, frequently surrounding spicules of old bone or portions of the fibrous connective tissue. Thin columns of epithelial cells, cut at right angles, looked like large giant cells in bone marrow spaces but special staining confirmed their true epithelial structure. Epithelial cords, two to three cells thick, were seen extending into the neighboring structures distant from the main tumor mass and surrounded on all sides by dense connective tissue. Infiltrations into tissue spaces and occasionally into lymphatics by contiguous growth were observed. Five animals showed tumor infiltration into the connective tissue and muscles of the cheek (Fig. 37); in four, the base of the tongue was invaded and in one the unaffected side of the mandible became involved, all by direct extension.

Local Destructive Properties. Expansion and distortion with resorption of the jaws were more characteristic of the cystic adamantoblastomas. Thin layers of cortical bone, in which evidence of pressure atrophy could be seen, surrounded the cysts in some cases. In others, the cystic expansions caused complete resorption of all peripheral bone. The little remaining soft tissues of the stroma were so compressed by the expanding forces of the cysts as to be difficult to recognize. Membrane linings were flattened and distended. The cheek and the muscles of the jaws were stretched to several times their normal size (Figs. 4, 6, 17, 40 and 41).

Local Interference with Function. The expansion of these tumors almost invariably caused displacement of the incisor and molar teeth, producing severe malocclusion. The tongue was forced into grossly abnormal positions. The tumor masses invaded the temporomandibular articulation and caused extensive destruction in these areas. These destructive invasive forces, together with the disabling effects on the muscles, greatly contributed to limiting function or even to complete loss of function of the jaws (Fig. 6).

Thus we see that if we insist that all four of the criteria laid down by

Ewing be present to pronounce a tumor "malignant," only 2 of the 97 pure adamantoblastomas may be thus classified. About one-third lacked only the metastatic feature to be truly "malignant," while about two-thirds lacked two of the four necessary requirements to be classified "malignant." These findings cast doubt on the oft repeated statement that the adamantoblastomas are benign.

Mitoses. Mitotic figures were not observed in the purely cystic types. The epithelial cells were well differentiated and bore no anaplastic qualities. In the more solid adamantoblastomas mitoses were few, and were observed only after careful search (Fig. 38). In the pure solid adamantoblastomas, while anaplasia was a prominent characteristic, only occasional mitotic figures were found. Mitoses were also infrequent in the metastases to the lymph glands.

TABLE II
Classification of Developmental Stages

- A. ADAMANTOBLASTOMA
 - 1. MONOCYSTIC
 - (a) Monolobulated
 - (b) Multilobulated
 - 2. MULTICYSTIC
 - (a) Without solid epithelial cell masses
 - (b) With solid epithelial cell masses
 - (1) Squamous cell form
 - (2) Epidermoid (with keratohyalin)
 - 3. SOLID ADAMANTOBLASTOMA
- B. SARCO-ADAMANTOBLASTOMA

Developmental Stages of Adamantoblastomas

My classification of the developmental stages is based on the morphologic and histologic characteristics of these tumors (Tables II and III). The general term, adamantoblastoma, amply covers all central epithelial tumors which were found in these mandibles. The morphologic features are classified as cystic, solid, or both, and if cystic, as to whether monocystic or multicystic. The histologic features are further amplified by describing the characteristic epithelial form (Table II). It will be noted that in the classification of the multicystic types the squamous and epidermoid forms are emphasized. I purposely omitted from this classification other subclassifications such as adenomatous, stellate and ameloblastic epithelial forms, basal cell or embryonal types because the presence of such cells was infrequent in my tumors. This omission does not exclude the possibility of these subclassified forms attaining the prominence that the epidermoid form did in my group. In such event they become 2(b)(3), etc., in my classification.

1. *Monocystic Adamantoblastoma.* This type of epithelial tumor

(Fig. 39) is a growth composed almost entirely of a single cyst, devoid of epithelial masses, with an occasional exception. The monocystic multilobulated type includes those tumors with two or more connected cyst lobules.

2. *Multicystic Adamantoblastoma*. The main feature of these epithelial tumors are their multicystic character. They are further subdivided into two subheadings: (1) containing epithelial masses in the form of nests, strands, cords, or sheets (Figs. 40 and 44); and (2) those devoid of such cells (Fig. 41). Keratin and pearl formations may also be found in members of this group of epithelial tumors (Fig. 7).

3. *Solid Adamantoblastoma*. These growths are devoid of cysts. They are composed of solid epithelial masses containing more anaplastic features. Keratohyaline structures were found in all of my cases,

TABLE III
*Distribution of 103 Classified Adamantoblastomas**

	No. of animals	No. of tumors
Monocystic monolobulated	39	52
Monocystic multilobulated	4	4
Multicystic, without solid epithelial masses	10	13
Multicystic, with solid epithelial masses	7	9
Multicystic epidermoid	15	16
Solid adamantoblastomas	3	3
Sarco-adamantoblastomas	6	6

<i>Other Tumors Observed</i>		
	No. of animals	No. of tumors
Odontomas	2	2
Sarcomas (pure)†	9	9
Ranula	1	..

* Seventy-two animals studied presented 114 tumors, of which 97 were pure adamantoblastomas, and 6 were sarco-adamantoblastomas.

† Of the 9 pure sarcomas, 5 were osteogenic, 2 spindle cell, 1 giant cell and 1 fibrosarcoma.

but such tumors without pearl formation would also fall in this classification (Fig. 42).

Sarco-adamantoblastomas

In six cases, sarcomas were found actively intermingled with the adamantoblastomas. This constitutes more than a rare finding and deserves to be classified separately (Figs. 22 and 46).

The foregoing classification, while based chiefly on the morphologic and histologic characteristics of these growths, may be further amplified through a consideration of both origin and malignancy. The origin, as has been pointed out, being the outer unspecialized epithelial cells of the enamel organ, makes possible the development of the diversified cell forms and modifications noted in my classification. In this respect

adamantoblastoma may be distinguished from "epitheliomas" which usually lack such diversification. It will be noted further that while the categorical arrangement of these growths depends upon their cystic or solid elements, there are also evident progressive degrees of malignancy, ranging from the benign purely cystic to the more malignant solid forms.

DISCUSSION

Development of Adamantoblastomas

A considerable number of tumors could not be classified definitely in a single specific category but possessed characteristics of two or more types of adamantoblastomas. Thus, not all solid tumors were 100 per cent solid nor were all those cited as cystic tumors purely cystic. Several monolobulated tumors showed epithelial extensions from their cystic linings with cystic formations in them. Thus, a monolobulated cyst was being transformed into one which was multilobulated. However, these epithelial extensions do not always break down. In many cases the proliferation gives rise to solid masses of cells occupying considerable areas and as such transforms the tumor from the purely cystic to the cystic-solid variety (Figs. 43 and 45). Some of the cystic masses may break loose from their parent monocystic growth which thus becomes transformed into the multicystic variety. Thus, the monocystic tumors, if allowed to grow, in some instances retain their own individual features during the entire growth period while in others they take on characteristics of adamantoblastomas higher in the scale of malignancy.

Cahn³⁹ reported a single-cysted dentigerous tumor which contained mural swellings of epithelial cells in the cystic lining. This, he believed, had the potentiality of proliferating and giving rise to an adamantoblastoma. Churchill³⁷ and Schroff³⁸ reported follicular cysts with adamantoblastomatous characteristics. Hankey¹⁷ described a multilocular cyst arising from what was thought to be a dental cyst. These cases in the literature tend to substantiate my observations of definite transformations in adamantoblastomas. This quality of transformation has been observed also in recurrences of human adamantoblastoma when second or third operations were necessary. Histologic study of the excised recurrent neoplasm frequently revealed more malignant features than the original. Lemaitre, Delater and Ardoin⁵¹ described two such cases. In one instance the recurrence still presented a few adamantine structures but the typical cell had changed into a form resembling the squamous epidermal type. While previously it had seemed well encapsulated, the recurrence penetrated the surrounding tissues and assumed all the qualities of an infiltrating epithelioma.

The adamantoblastoma does not always exercise its transforming capabilities in the direction of more malignant forms. The opposite tendency has also been observed in my mice. Multicystic tumors were seen wherein the trabeculae separating individual cysts were being actively resorbed, thus simplifying their cystic structure. I also found one solid adamantoblastoma which showed evidences of early cystic degeneration (Fig. 10). Robinson³⁶ and Robinson and Wallace⁷⁰ reported such a case in a human being which degenerated from the solid to the cystic form. It is my opinion that if irritative factors such as surgical or other mechanical trauma and secondary infections were avoided, more adamantoblastomas would normally undergo cystic breakdown with dissolution of their solid epithelial masses. This does not mean, however, that all adamantoblastomas begin as solid epithelial tumors and become cystic only through breakdown.

The observed transformations from cystic to solid or from solid to cystic forms, with the many intermediate stages, raise a question as to the validity of segregating adamantoblastomas into the categories commonly used. It is probable that the different features are merely stages in the development and the life cycle of an adamantoblastoma. If it is observed at one stage, it is called a cystic adamantoblastoma; if it is observed at another stage, it is called a solid adamantoblastoma.

Epithelial Cell Types in Adamantoblastomas

The hypothesis based on the morphologic characteristics of the adamantoblastomas that the various forms constitute stages in development rather than independent types is not contradicted by the variety of epithelial cell types found in these growths. The outer embryonic layer of the enamel organ from which spring the cells comprising these tumors is capable of differentiating into many cellular forms. These may give rise to special features of the adamantoblastoma but need not necessarily alter the basic characteristic of the growth. The characteristic basal, squamous, or embryonal cells may not have prevailed as such throughout the entire life history of the growth, but may have been converted from one form into another.

Geschickter²⁷ stated that the more primitive elements of the enamel organ may proliferate and differentiate in several directions, producing islands of enameloblasts, squamous cells and basal cells, a mixture of epithelial elements characteristic of adamantoblastoma. Gioia⁷¹ described a cystic adamantoblastoma lined by columnar epithelium. Moore⁵³ classified these tumors by cell type as cuboidal, columnar and stellate. Lemaitre, Delater and Ardoin⁵¹ described two cases of adamantoblastoma in which the typical cell was squamous epidermal in

solid sheets and with some keratinization. Adcock ⁷² presented a case of adamantoblastoma which was of the glandular cystic type. Sprawson and Keizer ⁶¹ described structures in such tumors which simulate the stellate reticulum of the enamel organ. Gentsch ²⁶ stated that all three types of enamel organ cells are represented in an adamantoblastoma; *i.e.*, the outer, flattened cuboidal cells, the intermediate layer of polygonal cells and the high cylindrical palisade cells which are the true ameloblasts. In the adamantoblastomas observed by these authors the various epithelial components are natural consequences of pluripotential embryonic origin with the possibility of giving rise to essentially all types of epithelial cells during the proliferative state. Ewing ¹⁵ maintained that these tumors are mainly of one nature and that the epithelial cells of adamantoblastomas, in exhibiting all variations in form between the stratified squamous epithelium and specialized adult ameloblasts, recall the changes traversed in the normal development of the enamel organ. Thoma, ⁷³ too, stated that adamantoblastomas may present a multitude of epithelial cell forms. He recognized such types as basal cell, adenoid, acanthoma and keratinizing.

Adenomatous structures observed in my adamantoblastomas never assumed the rôle of typical cells for any one tumor. Oral epithelium has the potential ability to form glandular as well as dental structures and, since the components of the enamel organ are derived from the epithelium of the oral cavity early in fetal life, the embryonic potentiality of giving rise to cells which may differentiate into adenoma-like structures may exist. The more specialized columnar epithelial cells, some well differentiated and others more anaplastic, give further evidence of the multipotential powers of differentiation of the outer epithelial cells of the enamel organ. The more frequent occurrence of the squamous cell type may be explained on the basis that the embryonic cells composing the outer layer of the enamel organ should tend to reproduce in a manner similar to their immediate parent cells, the oral epithelium.

Stroma

The various forms of stroma tend to portray the proliferative powers and malignant tendencies of the adamantoblastomas. For example, it was observed that richly cellular matrices and sarcomatous stromas were found in the more active-appearing tumors, in which infiltration and invasion of neighboring structures by long extensions of epithelial cells were prominent features. The solid adamantoblastomas invariably contained areas of fibroblastic stroma. Bauer ¹⁴ also recognized the significance of the connective tissue stroma. He noted that in the cystic types there is usually an insignificant increase of the connective tissue,

while in some of the more solid tumors the stroma is greatly increased and plays an important rôle.

The cystic forms of adamantoblastoma, types known to be slower growing and less active than those with large areas of solid epithelium, usually contained stroma composed largely of hyalinized connective tissue bundles, comparatively acellular. The picture here contrasted markedly with those tumors in which the stromal and epithelial proliferation gave definite signs of malignancy. The cellular quality of the connective tissue stroma varied directly with the epithelial proliferation in the solid portions of adamantoblastomas. Probably because of desmoplastic properties of the growths, the stroma of some of them is so activated that the connective tissue assumes sarcomatous features, or definite mixed tumors—sarco-adamantoblastomas—may develop as I have found in this series.

Formation of Enamel

Although it is frequently stated in the literature, I have never observed tumor-formed enamel in any of my adamantoblastomas. Kronfeld⁵ and Robinson⁷ stated that enamel is never formed in adamantoblastomas. Churchill³⁷ never observed amelogenesis in true adamantoblastomas. He stated that enamel formation is possible only when there is an arrangement of the differentiated cells similar to that present during the formation of a tooth. I observed enameloblasts as well as cells of the stellate reticulum and stratum intermedium in the solid epithelial portions of these tumors in mice, but evidence of functional activity was never seen. The lack of tumor-formed enamel in pure adamantoblastomas is to be expected because enamel is deposited only when it has been preceded by, and is in the presence of, already formed dentin or a similar structure. Since dentin, which is of connective tissue origin, is not formed in an epithelial tumor such as the adamantoblastoma, the formation of enamel, dependent on the presence of dentin, must be and is precluded.

However, two growths were found which did contain tumor-formed enamel in conjunction with tumor-formed dentin (Figs. 47 and 48) arranged with wild, disordered patterns. Many individual neoplastic enamel organs of various sizes and shapes were seen, with the active production of enamel about previously formed dentin. There were proliferations of dentinoblasts within the crescent-shaped enamel organs and in many instances pre-dentin had been deposited but enamel formation had not yet begun. These two tumors, showing neoplasia of both epithelial and connective tissue, were true *odontomas* and should not be confused with the pure epithelial adamantoblastomas.

Malignancy

Adamantoblastomas are not benign growths if we accept Ewing's¹⁵ criteria for malignancy. We find that adamantoblastomas do not remain localized and circumscribed. They exhibit features which are diametrically opposed in character to benign growths. The adamantoblastoma is an infiltrative growth. Its epithelial columns and strands invade surrounding bone marrow spaces, the ramus of the mandible, the masseteric muscles, the base of the tongue and even spread to the opposite half of the mandible. This tumor possesses the power of destroying regional tissues. Resorption of bone takes place over extensive areas by the massive cystic expansions and pressure of proliferating epithelial sheets.

While my investigation of these tumors of mice could not include a study of the possibility of recurrent growths after removal, Robinson,⁷ in a review of 379 cases of human adamantoblastomas, recorded 119 in

TABLE IV

	Mice (97 adamantoblastomas found in the group of mice)		Man (397 cases in Robinson's ⁷ review of the literature)	
	<i>Number</i>	<i>Percentage</i>	<i>Number</i>	<i>Percentage</i>
Invasive growths or recurrent growths	30	30.9	119	31.4
Metastatic growths	2	2.1	9	2.4

which there were from one to as many as twenty-two recurrences. Recurrences are possible because of the invasive characteristics, negating the likelihood of complete surgical removal. There are cases on record where complete resection of a mandible was followed by recurrence. Benign growths do not exhibit these invasive qualities nor the same tendency to recur. If we consider the degree of infiltration and invasion in my animals, we find that similar recurrence would have been possible. Thus, out of a total of 97 pure adamantoblastomas, 30, or 30.9 per cent, exhibited the quality of invasion into the surrounding tissues (Table IV). This figure compares favorably with Robinson's 119 recurrences in 379 cases (31.4 per cent) and emphasizes the idea that the infiltrating quality of these tumors predisposes to recurrences.

Robinson⁷ recorded 9 metastasizing tumors in 379 cases reported in the literature (2.4 per cent). This compares favorably with my 2 cases with metastases, which is 2.1 per cent of my series.

However, Stout¹⁶ maintained that for practical purposes the probability that any given adamantoblastoma will metastasize is negligible. While this statement is borne out in my series, nevertheless the fact that metastases do occur furnishes further evidence against considering

these growths benign. Robinson⁷ considered these tumors as persistent but not malignant. It must be pointed out that persistency is a trait of malignant tumors.

I have observed in my experimental group tumors duplicating in all respects the extensive variety of human adamantoblastomas. They are similar in morphology, cellular constituents, destructive actions, invasions and metastases. In many respects they are identical. Thus, that which applies to my experimental group may be said to hold for this tumor in man. From my observations, adamantoblastomas must be considered not as purely benign tumors, but as *locally malignant tumors* with a slight potentiality to metastasize.

Origin

In considering the site of origin of adamantoblastomas, those reported in the literature are based, of necessity, on limited observations because of the surgical nature of the human material studied and the embryologic difficulties involved. In spite of these limitations certain definite ideas prevail, the most common one being that the epithelial rests are the site of origin. Since the time of Malassez' original observation of the presence of these rests in the peridental membrane of teeth, there has been a steady stream of reports in the literature pointing to these rests as the source of origin of adamantoblastomas. Malassez himself did not report actual observations of tumors arising from epithelial cell nests. He merely assumed that these epithelial structures might proliferate and give rise to tumors. Yet, many authors who followed took it for granted that these rests were the actual source of the growths which they reported and so stated in their reports.

In my study I was especially apprehensive concerning this possibility, searching carefully for any sign of proliferation of the epithelial rests or even contiguous location of an adamantoblastoma to one of them. In most of my cases, epithelial rests were not found, and in those few cases where they were observed they were conspicuously inactive. Not a single adamantoblastoma was observed contiguous to these rests in the peridental membrane. In fact, nearly all of my tumors were actually in a position diametrically opposed to the location of epithelial rests. In no possible way could they have originated from these structures in the peridental membrane. From these observations, we may definitely rule out the epithelial rests of Malassez as a source of origin of adamantoblastomas in this group of mice.

A little more weight may be given to the observations citing the oral epithelium as the source of origin. Von Bakay,³² Kuru,³³ Kaufmann³⁴ and, more recently, Cahn⁷⁴ reported cases of this type. In my own

series of animals I observed eight cases in which there were definite attachments of the adamantoblastomas to the oral epithelium. But these eight tumors had other points of attachment, *i.e.*, to the outer epithelium of the enamel organ. It is more probable that this latter point of attachment was the true site of origin since similar tumors in this series were so attached without being continuous with the oral epithelium. Attachment to the oral epithelium is apparently a secondary manifestation caused by traumatic or irritative ulceration of the oral surfaces, thereby providing an opportunity for stimulating the proliferation and downgrowth of the oral epithelium which in turn becomes attached to the adamantoblastoma. In the cases reported in the literature, only portions of the adamantoblastomas could be examined, hence the possibility of another site of attachment in those cases could not be ascertained. These observations, then, cannot compare with mine where it was possible to study the whole growth *in situ*.

The possibility of these growths arising from the epithelium of odontogenic cysts is in accord with my own findings. However, since it is my opinion that odontogenic cysts are merely stages in the development of adamantoblastomas, the proliferation of their epithelial linings may be considered as extensions or modes of transformations rather than as sources of origin. This study provides ample evidence to show that the outer embryonal epithelium of the enamel organ is the source of origin of these growths and may be considered as the only source of origin of the adamantoblastomas found in my animals.

"Adamantoblastomas" of Other Parts of the Body

Geschickter²⁷ stated that the occurrence of adamantoblastomas in the hypophyseal stalk and in the tibia is against the specificity of the enamel organ as a source for these growths. This idea would apply to the ameloblasts, cells of the stratum intermedium and the stellate reticulum as sources of origin. These specialized cells of the enamel organ would have to undergo metaplasia in order to form tumors such as I found. However, I do not believe that adamantoblastomas are due to metaplasia of such cells. The fact that tumors simulating the adamantoblastoma of the jaw have been found in the hypophyseal stalk and in the tibia does not detract in any way from my views as to origin, because of the embryonal character of the fourth layer of the enamel organ which I have designated as the source of the adamantoblastoma in jaws.

That the pituitary duct arises as an invagination of the oral epithelium amply explains the possible similarity of the two types of epi-

thelial tumors under discussion. They both maintain their embryonic character, and both may differentiate into a variety of epithelial cell forms, as stated in the literature. It should be borne in mind that neither in the adamantoblastoma of the jaws nor in the adamantoblastoma of the hypophysis are formed tooth elements found. The few adamantoblastomas found in the tibia likewise do not contain formed tooth elements and their presence may also be explained on the basis of abnormal embryonic epithelial invaginations. Thoma,⁸ Drummond,⁴⁶ Ryrie⁷⁵ and Oberling, Vermes and Chevereau⁷⁶ concur in this view. Whether these cells of origin represent isolated structures such as cell rests or epithelial implants, or whether they comprise a portion of a known anatomic formation such as the hypophyseal stalk, cranio-pharyngeal duct, or the enamel organ is not of essential importance. What is important is that they arise from similar epithelial parents, *i.e.*, stratified squamous epithelial structures, and that they retain similar embryonic qualities and multipotential powers in their growth tendencies.

Sarco-adamantoblastomas

There is no doubt that the sarco-adamantoblastoma is a distinct entity. These mixed tumors contain the morphologic and histologic structure of the sarcoma and the adamantoblastoma. Whether the sarcomatous features develop as a result of a desmoplastic action by the adamantoblastoma and are therefore secondary, whether the reverse is true, or, whether both begin simultaneously I cannot support with indisputable microscopic evidence. I am inclined to believe, however, that the sarcomatous manifestations are secondary to the original adamantoblastoma since I found epithelial tumors with sarcoma-like stroma, probably representing an intermediate stage. In several instances it was difficult to differentiate adamantoblastoma with a sarcomatous stroma from sarco-adamantoblastoma.

Are Dentigerous, Follicular and Multilocular Cysts Forms of Adamantoblastoma?

Although some authors believe these to be distinct entities, in no way related to adamantoblastomas, it is my opinion that dentigerous, follicular and multilocular cysts are stages of adamantoblastomas and comparable to the pure monocystic and multicystic stages of tumors found in my mice. In them, simple cystic growths present the same morphologic and histologic features and may or may not envelop the crown of a tooth (Figs. 43 and 49). The origin in the outer epithelial layer of the enamel organ is the same for these purely cystic tumors as

for those higher in the scale of malignancy. It has been noted that the epithelial linings of dentigerous cysts may proliferate and lead to adamantoblastomatous growths.

CONCLUSIONS

One hundred and three adamantoblastomas, found in a group of 79 mice with hereditary tumor tendencies obtained from the Slye colony at the University of Chicago, served as a basis for this report. In each instance the animal was allowed to live its normal life span. These adamantoblastomas were cystic, solid, or both cystic and solid.

From observations upon this group of adamantoblastomas it is concluded that:

1. Odontogenic cysts are stages in development of the adamantoblastoma.
2. Types of pure adamantoblastomas are not independent varieties but must be considered as stages in the development of these growths.
3. Enamel is never formed in pure adamantoblastomas.
4. The assertion that "adamantoblastomas" are found in other parts of the body in no way refutes the conclusion that adamantoblastomas of the jaw arise from the enamel organ of a tooth.
5. The point of origin of adamantoblastomas in the jaw is the group of embryonal cells comprising the outer epithelial layer of the enamel organ.
6. Adamantoblastomas are not characterized by the features usually ascribed to benign growths. They do, however, possess either one or more of the criteria for malignancy. Therefore, they should be designated as locally malignant with a slight potentiality to metastasize.

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DESCRIPTION OF PLATES

PLATE 4

- FIG. 1. Lateral radiographic view illustrating extensive involvement of bilateral tumors. Mouse 20. (A) Area of previous excision for biopsy. (B) Large cystic portion of tumor outlined by arrows. (C) Tremendous elongation of incisor teeth due to malocclusion; these tend to form circular structures by their continuous growth. (Normal mandibular outlines are obliterated by the tumors which cause bone resorption. The ramus in this view has been destroyed.) $\times 4$.
- FIG. 2. Ventral radiographic view illustrating bilateral cystic adamantoblastomas. Mouse 36. (A) Monocystic multilobulated adamantoblastoma with bone septa clearly distinguishable. (B) Displacement of lower incisor teeth by expansive tumor growth. (C) Elongation and malocclusion of incisor teeth. (D) Monocystic adamantoblastoma. (Note the outward expansiveness of the growth.) Tumor diagnoses were made following histologic study. $\times 4$.

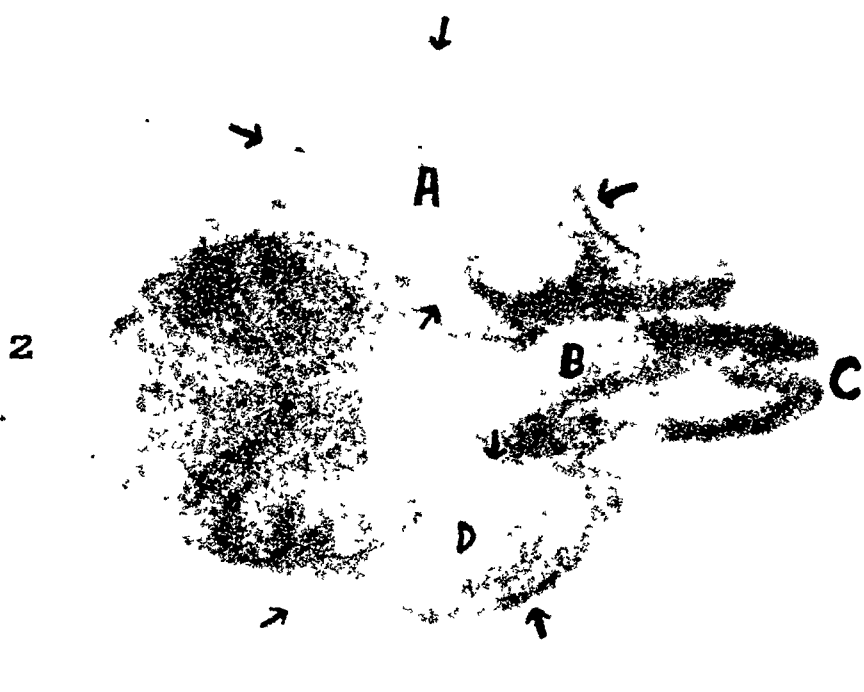


PLATE 5

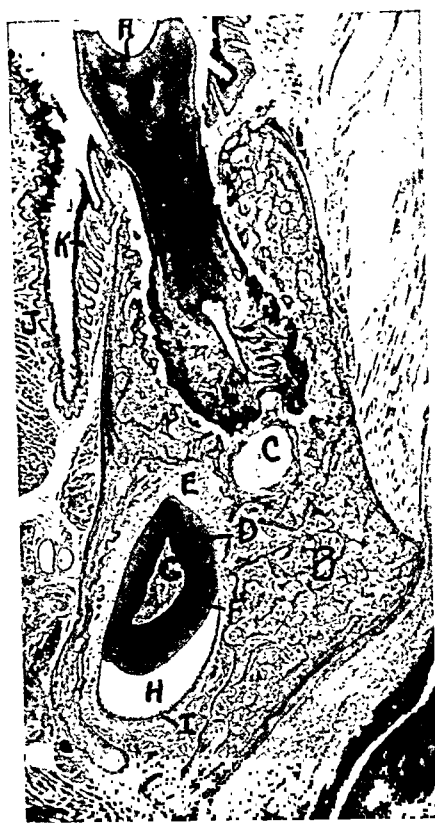
FIG. 3. Cross section (all photomicrographs are cross sections unless otherwise stated) showing normal structures of the mandible. Mouse 7. (A) Molar tooth. (B) Body of mandible. (C) Mandibular canal. (D) Cross section of unerupted portion of incisor tooth. (E) Peridental membrane. (F) Dentin. (G) Pulp of tooth. (H) Enamel space. (I) Enamel organ. (J) Tongue. (K) Oral mucous membrane. $\times 22$.

FIG. 4. Marked distortion of tooth contour. Mouse 20. (A) Marked distortion of cross section of incisor tooth simulating a longitudinal section. (B) Irregularly shaped and placed enamel space. (C) Multicystic solid adamantoblastoma. (D) Lengthening and atrophy of striated cheek muscles. (E) New bone formation surrounding the tumor. (F) Inflammatory masses in cysts. (Note the loss of normal bone outlines when compared to Fig. 3.) $\times 12$.

FIG. 5. Cystic characteristics. Mouse 31. (A) Stratified squamous epithelium lining the cyst. (B) Desquamated epithelial cells. (C) Cholesterol slits. (D) Inflammatory masses. (E) Hemorrhagic debris. (F) Foam cells. (G) Artefact. (H) Enamel space. (I) Dentin. (J) Stroma. $\times 160$.

FIG. 6. Cystic characteristics. Mouse 10. Ramus region. Multicystic adamantoblastoma showing (A) multicystic character. (B) Bone septa. (C) Stratified squamous epithelium lining the cysts. (D) Clear cystic fluid. (E) Inflammatory cystic exudate. (F) Displaced incisor tooth. (G) Destruction of ramus by the invasion of neoplastic tissue. (H) New bone formation at periphery of cysts. (I) Lengthening and stretching of striated muscles. (Note loss of normal bone outlines.) $\times 11$.

3



4



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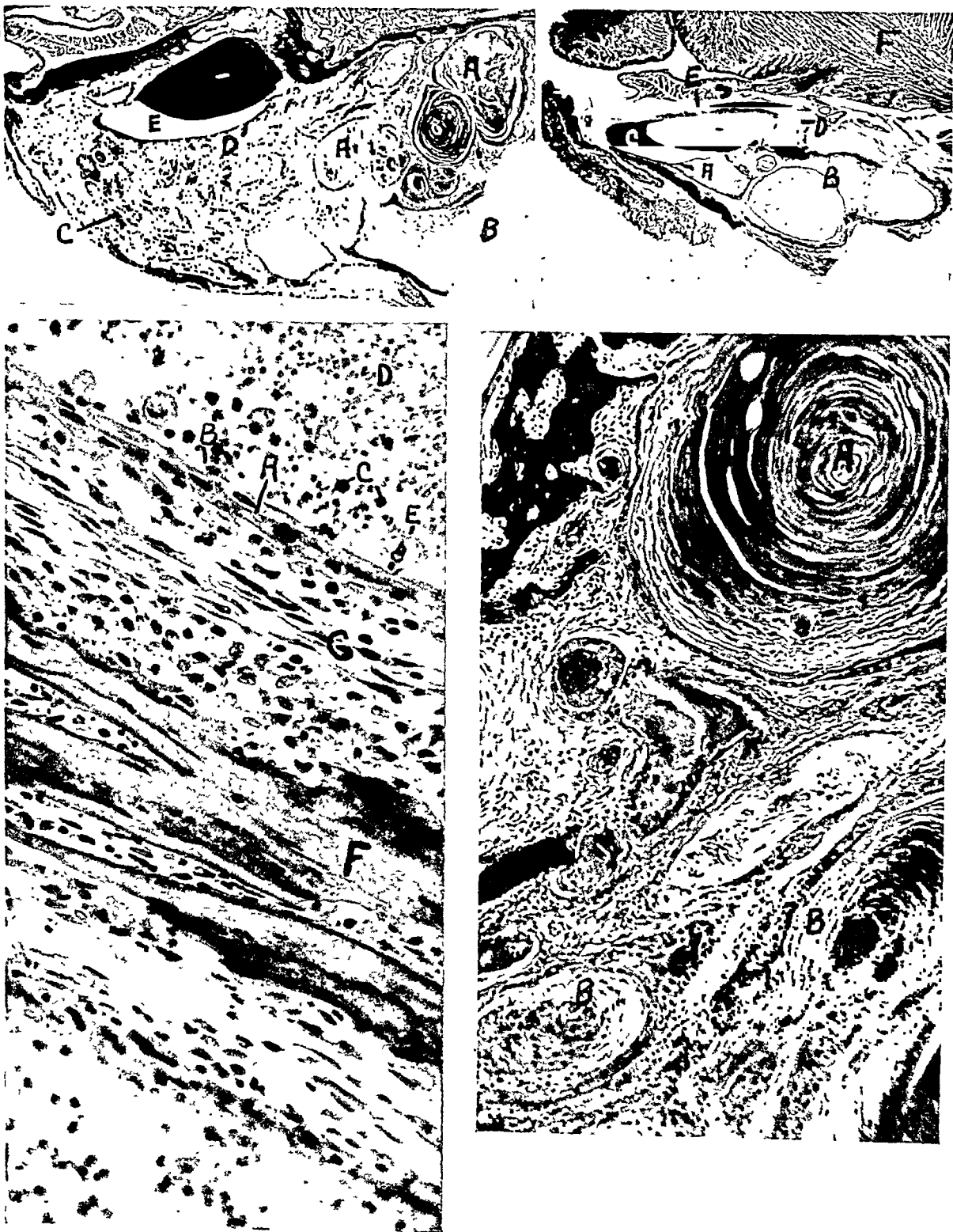
PLATE 6

FIG. 7. Longitudinal section of multicystic epidermoid adamantoblastoma. Mouse 62. (A) Keratohyaline structures, some in the process of dissolution with the degenerative masses tending to form cysts. (B) Region of previous excision for biopsy. (C) Epithelial sheets and cords, branching and anastomosing. (D) Attachment to the enamel organ. (Note: The tumor is below and posterior to the enamel space, "E.") $\times 13$.

FIG. 8. Longitudinal section showing growth below and posterior to the enamel space and tooth. Mouse 43. (A) Attachment to the enamel organ. (B) Multicystic solid tumor. (C) Enamel space. (D) Incisor tooth. (E) Peridental membrane. (F) Tongue. $\times 10$.

FIG. 9. Cystic characteristics. Mouse 10. (A) Cyst lining composed of flattened, lengthened stratified squamous cells. (B) Desquamated epithelial cells. (C) Inflammatory cells. (D) Hemorrhage. (E) Foam cells. (F) Bone septa with (G) fibrous connective tissue stroma. $\times 350$.

FIG. 10. Keratohyaline structures. Mouse 51. (A) Epithelial pearls. (B) Beginning cystic breakdown. $\times 155$.



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PLATE 7

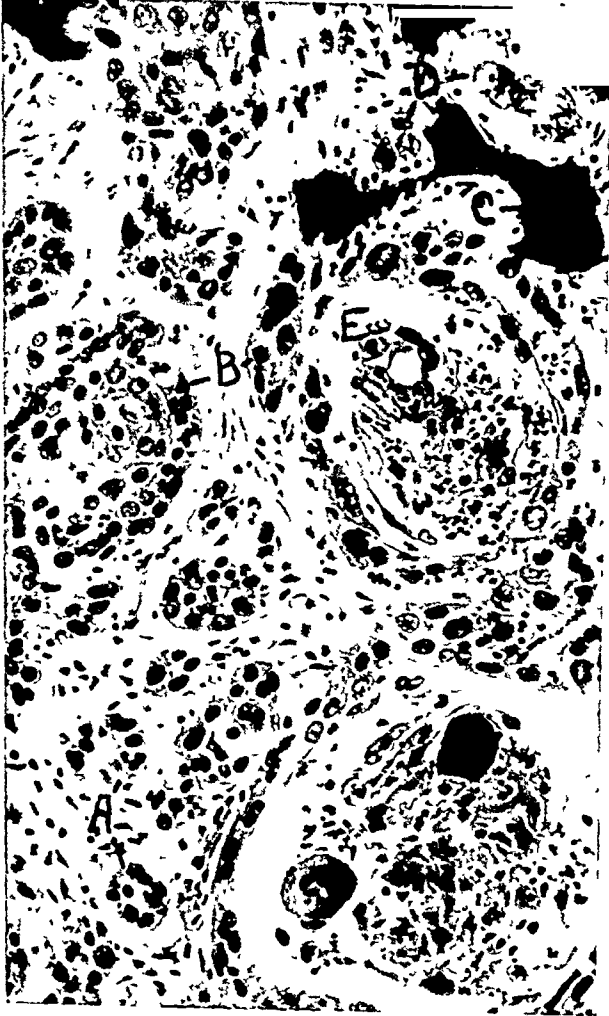
FIG. 11. Solid epithelial characteristics. Mouse 13. (A) Enamel space. (B) Stratified squamous epithelium with intercellular bridges. (C) Epithelial extensions and cords permeating the surrounding stroma. $\times 255$.

FIG. 12. Solid epithelial characteristics. Mouse 9. (A) Epithelial extension from cystic lining. (B) Cross sections of epithelial cords. (C) Undifferentiated-appearing epithelial masses. (D) Alveolar or stellate arrangement. $\times 195$.

FIG. 13. Solid epithelial characteristics. Mouse 19. (A) Adenoma-like epithelial cells. (B) Hyperchromatic nuclei. (C) Bone spicules in process of resorption. (D) Osteoclast in Howship's lacunae. (E) Central cystic breakdown of solid epithelial portions. $\times 255$.

FIG. 14. Solid epithelial characteristics. Mouse 57. (A) Undifferentiated basal-like epithelial cells, carcinomatous in appearance. (B) Bone spicules in process of resorption. (C) Hyperchromatic nuclei. (D) Epithelial mass undergoing cystic breakdown. $\times 145$.

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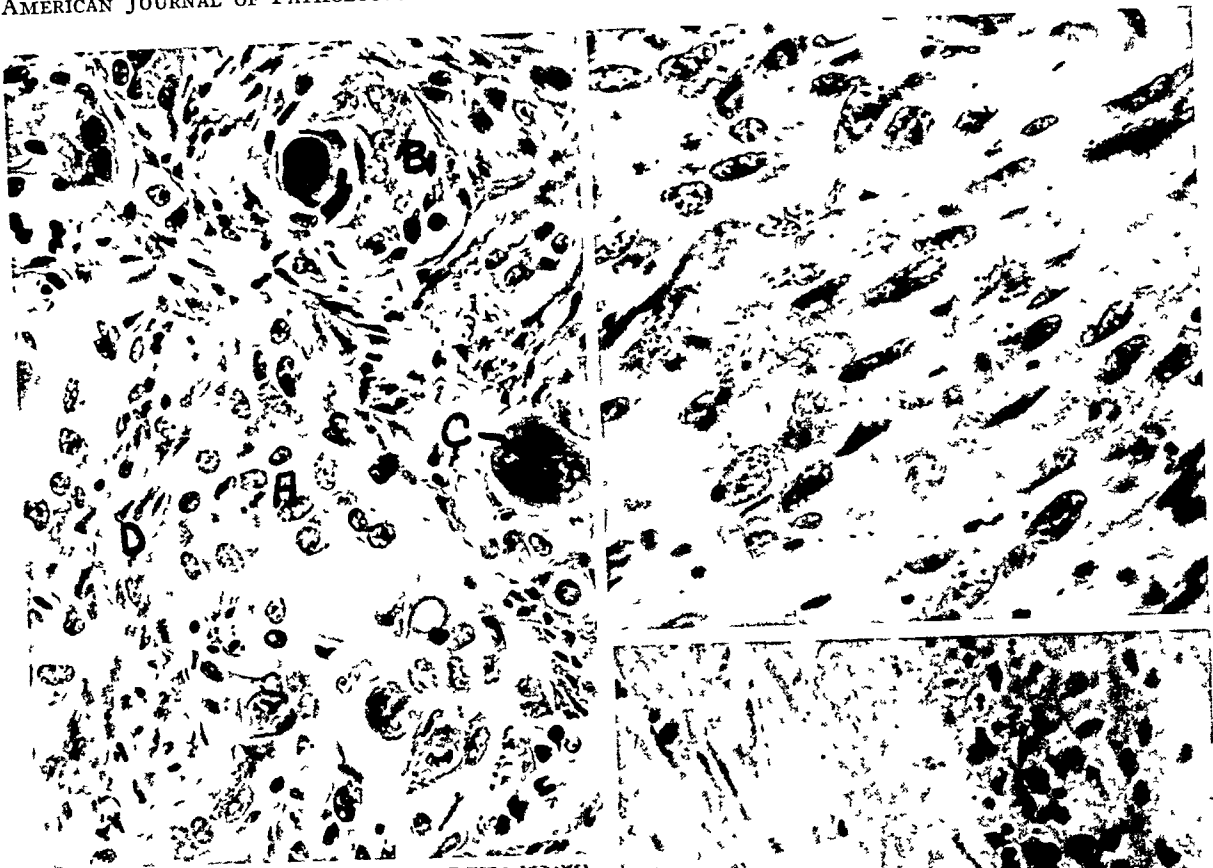
PLATE 8

FIG. 15. Solid epithelial characteristics. Mouse 16. (A) Embryonal epithelial syncytium with anaplastic features. (B) Cross-section of epithelial strand simulating a giant cell. (C) Foreign body giant cell. (D) Stroma. (There is very little stroma present.) $\times 395$.

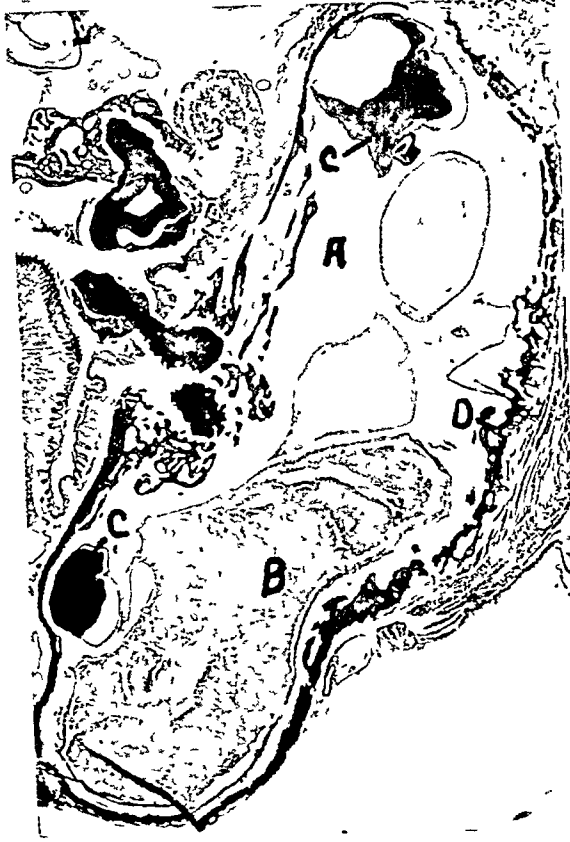
FIG. 16. Epithelial pattern simulating spindle cell sarcoma. Mouse 38. $\times 590$.

FIG. 17. Hyalinized collagenous stroma. Mouse 20. (A) Hyalinized stroma of a multicystic solid adamantoblastoma. (B) Hemorrhagic cystic content. (C) Displaced portions of incisor tooth. (D) New bone formation at periphery of tumor. (Note expansiveness of tumor with consequent effect on masseter muscles.) $\times 12$.

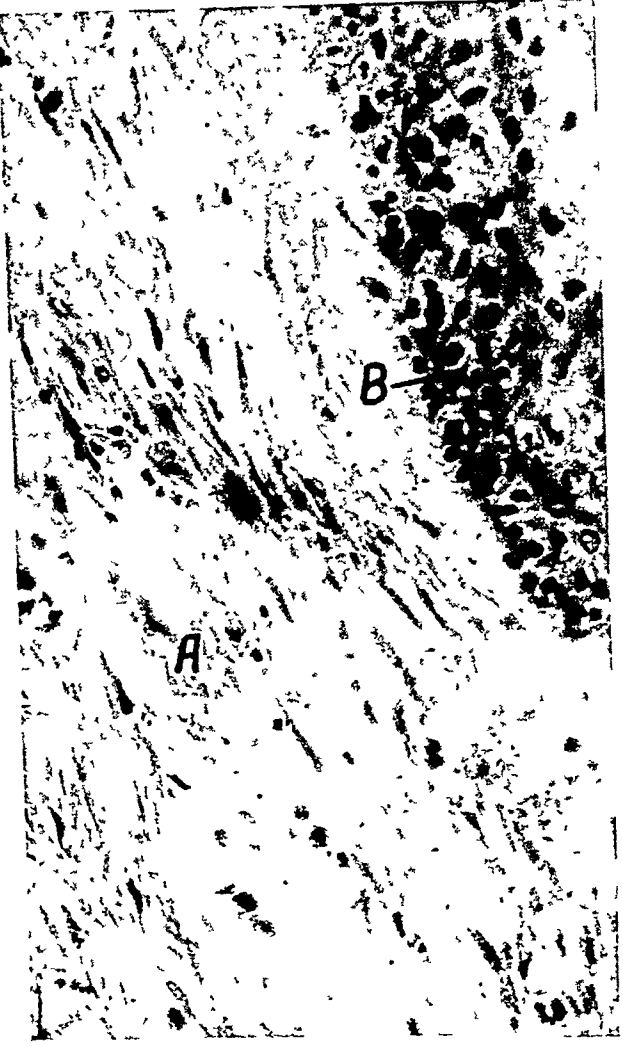
FIG. 18. High-power photomicrograph of Figure 17. (A) Hyalinized stroma. (B) Cystic lining. (Vascularity is minimal.) $\times 460$.



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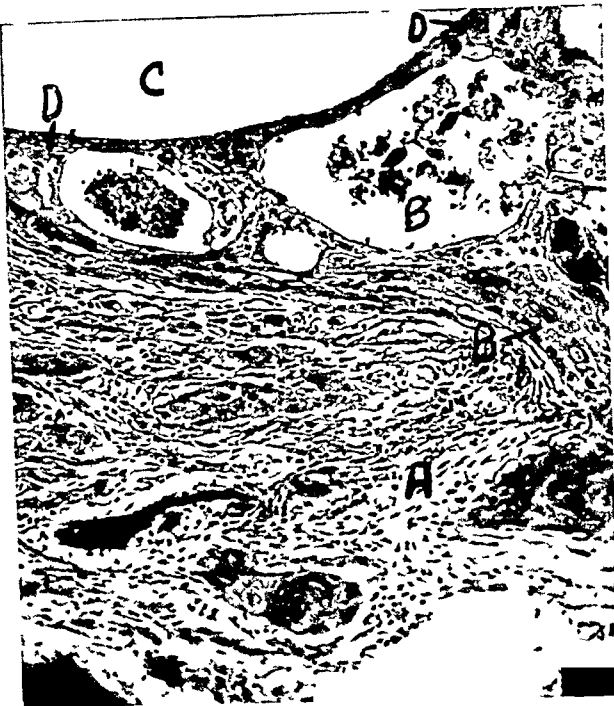
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PLATE 9

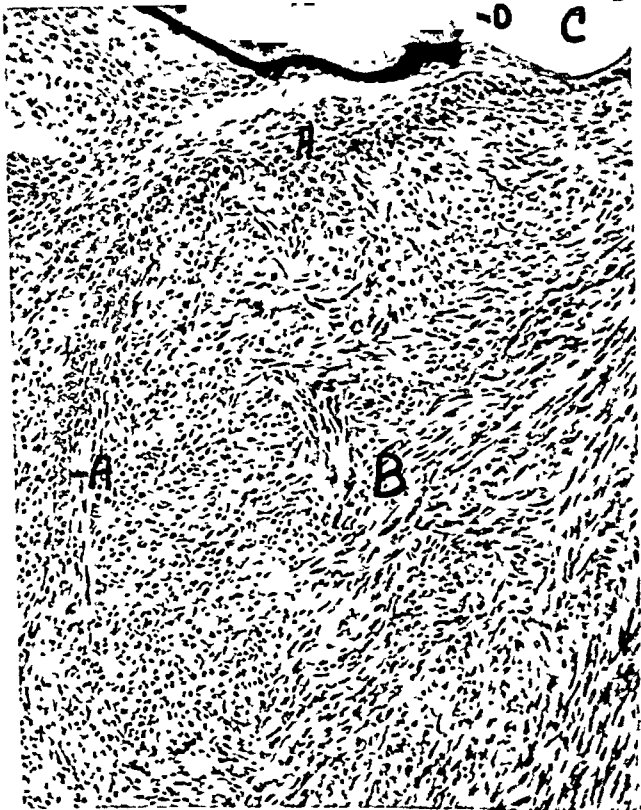
- FIG. 19. Cellular stroma. Mouse 59. (A) Cellular stroma. (B) Stratified squamous epithelial strands with cystic breakdown. (C) Enamel space. (D) Attachment of tumor to enamel organ. $\times 160$.
- FIG. 20. Sarcomatous stroma. Mouse 38. (A) Sarcoma-like stroma. (B) Infiltrating epithelial strands. $\times 280$.
- FIG. 21. Rich vascularity simulating an hemangioma. Mouse 38. (A) Rich capillary networks. (B) Fibrocellular stroma. (C) Enamel organ with outer embryonal epithelial cells at "D." (E) Hemosiderin granules. $\times 192$.
- FIG. 22. Desmoplastic characteristic. Sarco-adamantoblastoma. Mouse 17. (A) Epithelial proliferation from outer layer of cells of enamel organ. (B) Spindle cell sarcoma. (C) Enamel space. (D) Dentin. $\times 134$.



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PLATE 10

FIG. 23. Epithelial rest in peridental membrane with proliferation from the enamel organ forming an adamantoblastoma. Mouse 12. (A) Inactive epithelial rest in peridental membrane on the concave side of the tooth. (B) Proliferative mass from outer layer of cells of the enamel organ, on the convex side of the tooth. (C) Enamel space. (D) Dentin. $\times 105$.

FIG. 24. High-power photomicrograph of Figure 23. (A) Inactive epithelial rest in peridental membrane of a tooth of which the enamel organ gave rise to an adamantoblastoma. (B) Peridental membrane fibers. (C) Dentin. $\times 1315$.

FIG. 25. Developing normal incisor. Mouse 10. (A) Outer layer of embryonal epithelial cells of the enamel organ which are considered the origin of adamantoblastomas. (B) Enameloblasts. (C) Decalcified remnant of enamel. (D) Dentin with dentinal tubules. (E) Odontoblasts of pulp. (F) Shrinkage artefact. $\times 460$.

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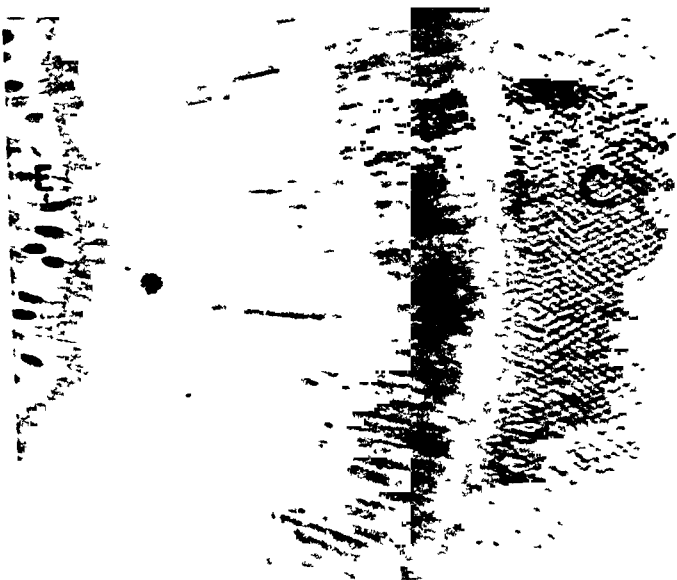


PLATE II

FIG. 26. Origin of adamantoblastomas. Mouse 30. (A) Proliferation of the outer epithelium of the enamel organ forming an adamantoblastoma. (B) Enamel space. (C) Dentin. $\times 183$.

FIG. 27. Origin of adamantoblastomas. From the same animal as shown in Figure 26 but at a more posterior level, showing a more advanced stage of development. (A) Beginning cystic breakdown. $\times 240$.

FIG. 28. Origin of adamantoblastomas. Mouse 36. (A) Epithelial proliferations arising from the enamel organ at several points. (B) Early stage in the development of a simple monocystic adamantoblastoma with attachments to the enamel organ. (C) Enamel space. (D) Cystic space. (Proliferations are below the enamel space, on the convex side of the tooth.) $\times 15$.

FIG. 29. Origin of adamantoblastomas. Mouse 10. (A) Extremely broad surface attachment where almost the entire outer layer of enamel organ is involved as the site of origin. $\times 240$.

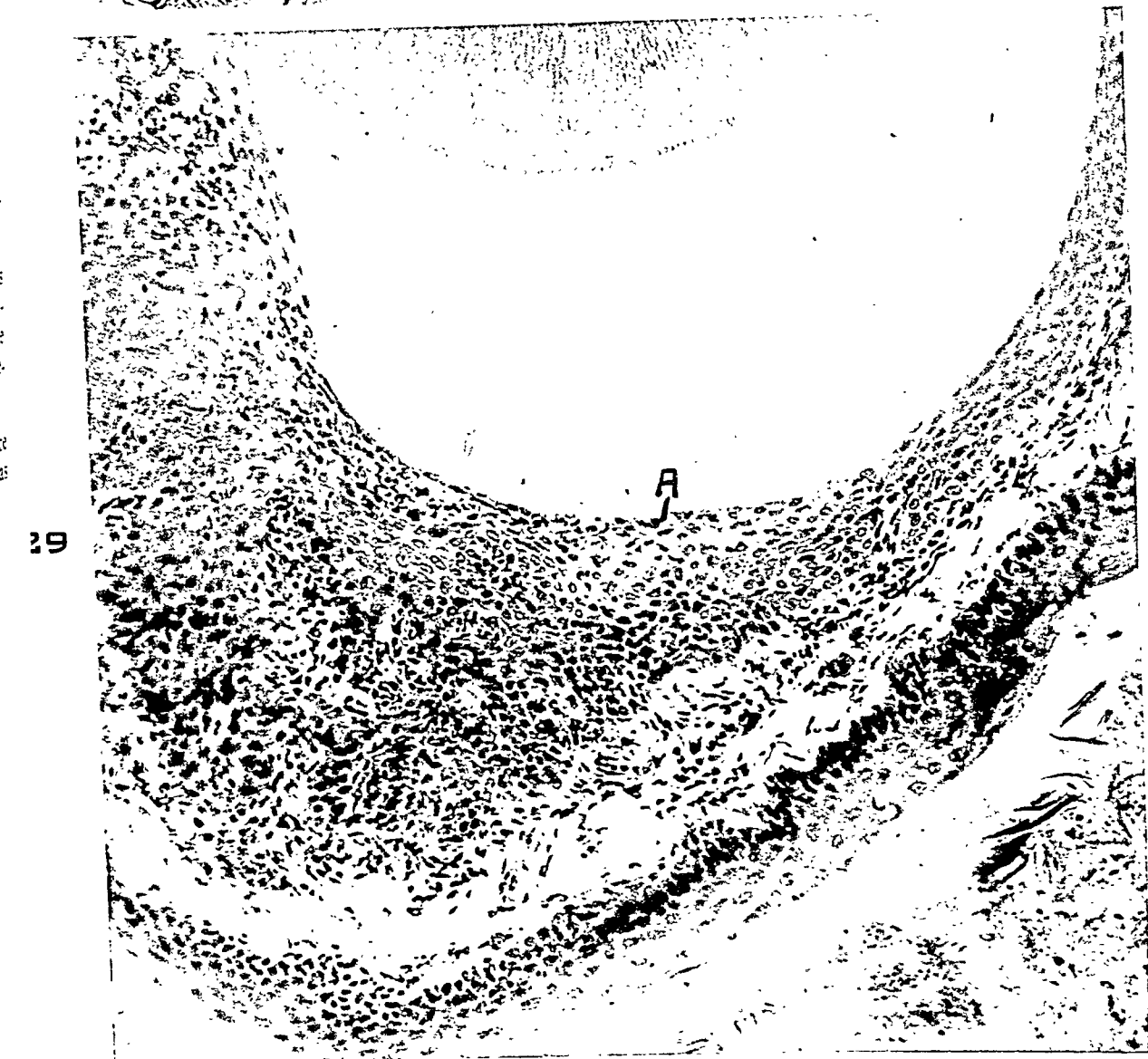
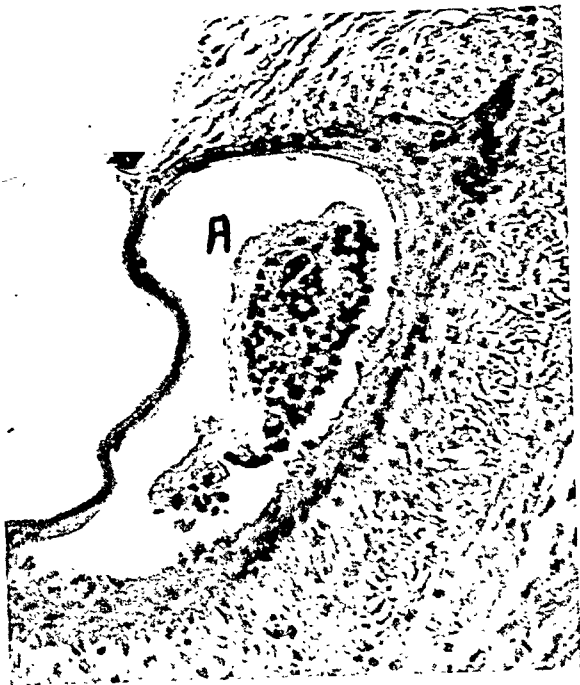
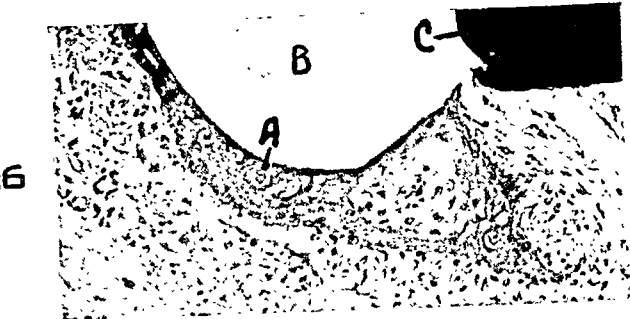


PLATE 12

FIG. 30. Origin of adamantoblastomas. Mouse 36. Multiple sites of origin from the outer layer of the enamel organ. $\times 150$.

FIG. 31. Origin of adamantoblastomas. Mouse 35. (A) Attachment of tumor of the enamel organ outside the enamel space. (B) Inflammatory exudate in cyst. $\times 85$.

FIG. 32. Origin of adamantoblastomas: carcinomatous. Mouse 38. (A) Attachment at point of origin to the enamel organ. (B) Squamous cell carcinomatous character of the tumor. (C) Beginning cystic breakdown of epithelial masses. (D) Enamel space. (E) Dentin. (F) Peridental membrane without involvement. $\times 105$.

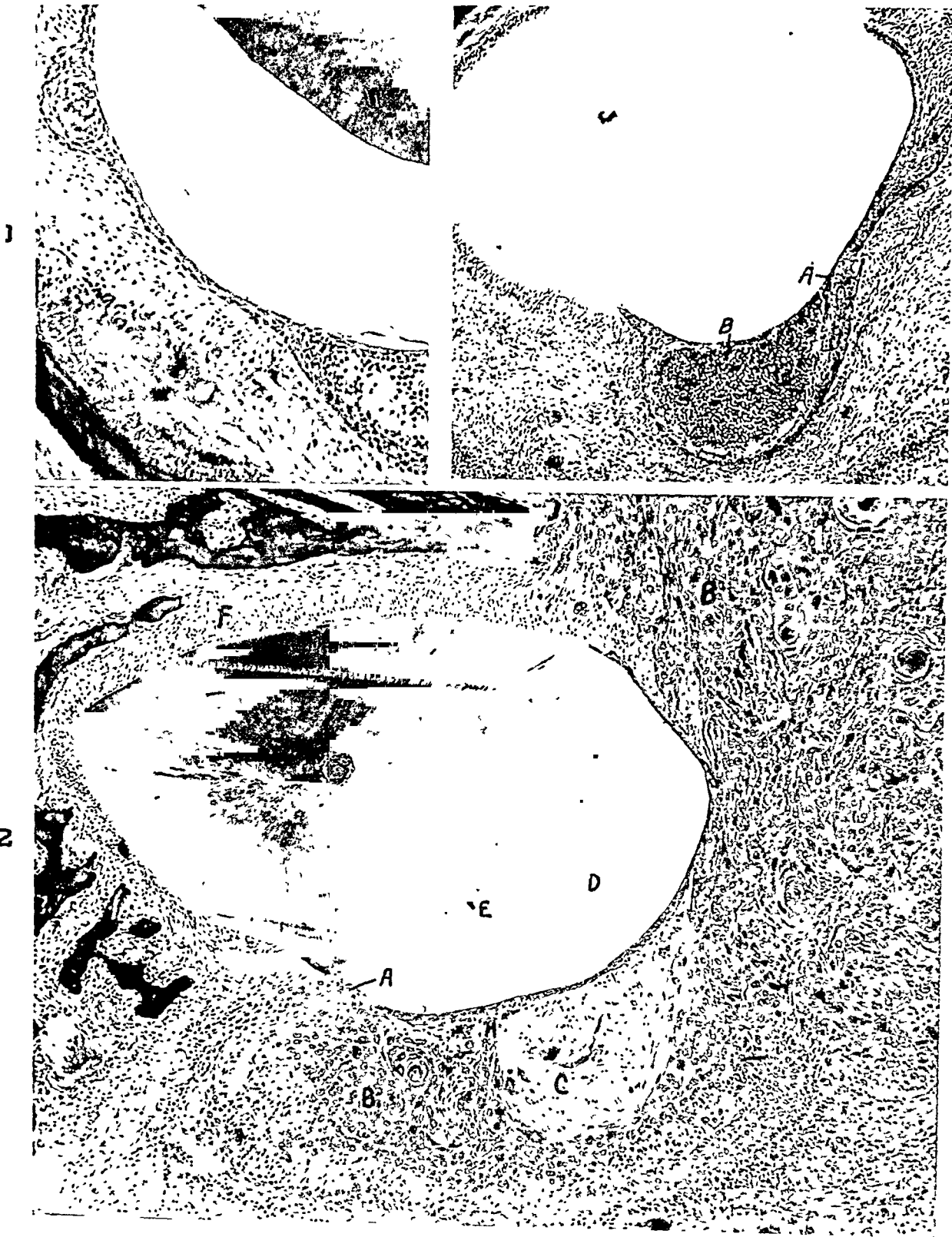
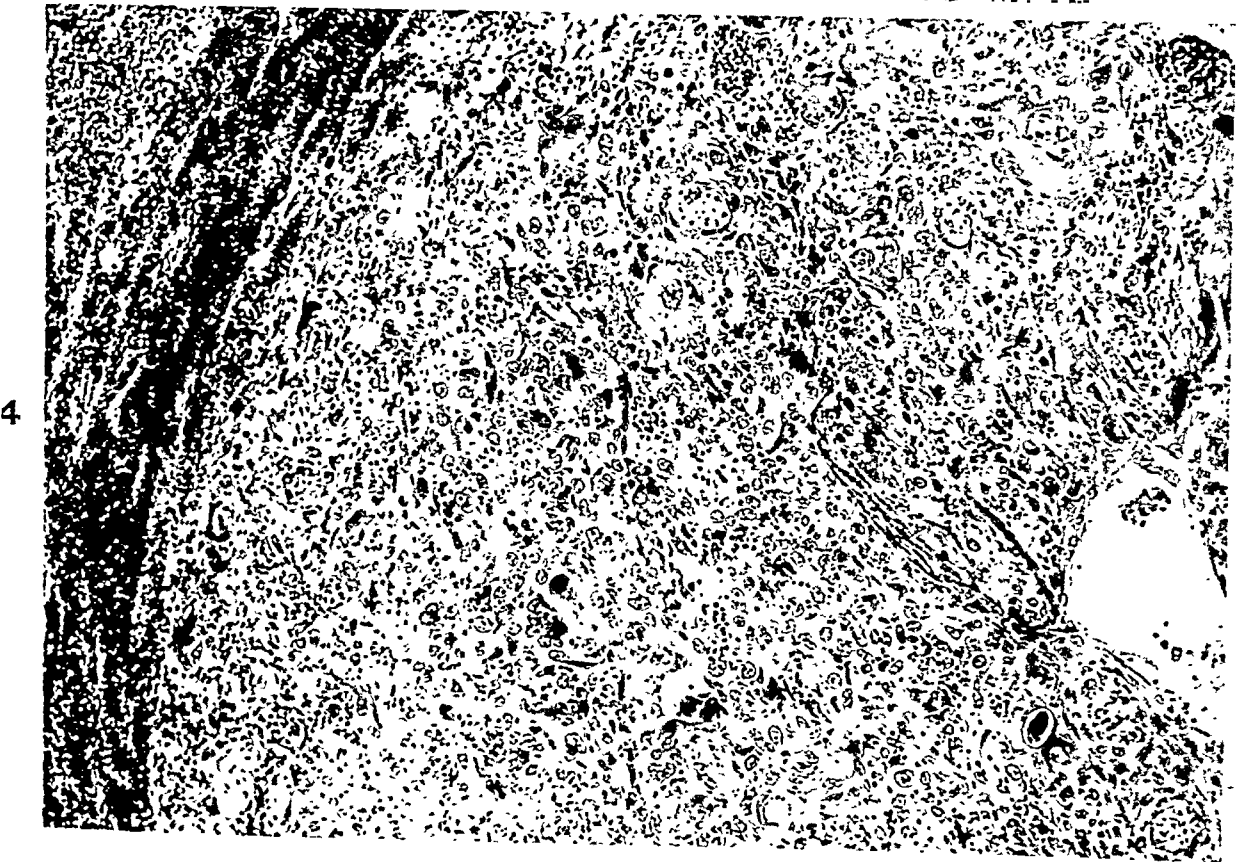
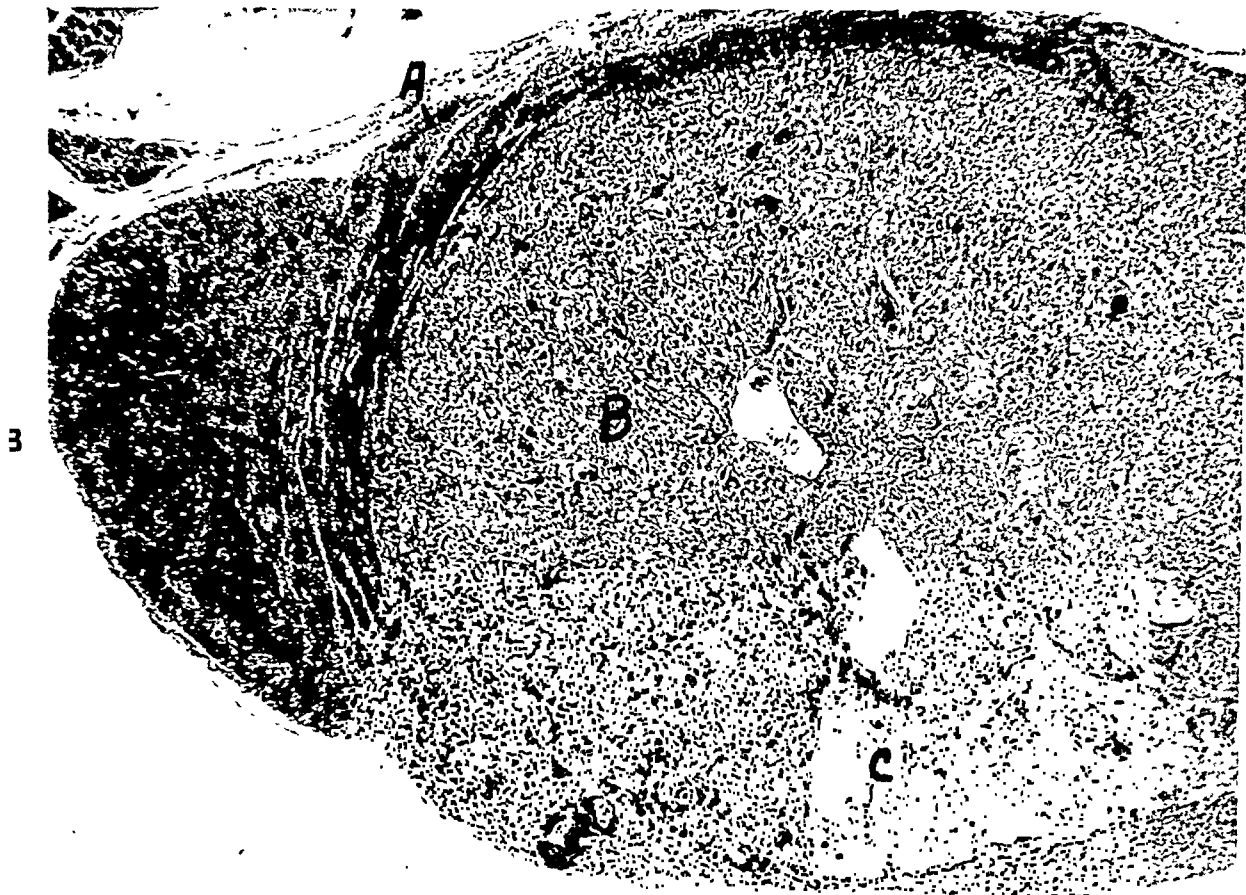


PLATE 13

FIG. 33. Metastasis in a lymph node. Mouse 38. (A) Compressed lymphoid structures. (B) Metastatic multicystic epidermoid adamantoblastoma. (C) Cystic breakdown in the metastasis. $\times 36$.

FIG. 34. Metastasis in a lymph node. High-power view of Figure 33. (The more anaplastic-appearing epithelial cells should be compared with Figure 16 which is the parent tumor.) $\times 135$.



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PLATE 14

FIG. 35. Invasion of tumor into surrounding bone. Mouse 40. (A) Epithelial tumor strands from a solid epidermoid adamantoblastoma invading surrounding bone structures. (B) Keratohyaline formations. (C) Evidences of very early cystic breakdown of epithelial masses. $\times 175$.

FIG. 36. Invasion of tumor masses into bone spaces. Mouse 72. There are wild, bizarre epithelial patterns. $\times 145$.

FIG. 37. Infiltration of tumor into muscle. Mouse 57. $\times 208$.

FIG. 38. Mitotic figures. Mouse 57. Epithelial strands of a multicystic epidermoid adamantoblastoma with cells in various phases of mitosis. $\times 1260$.

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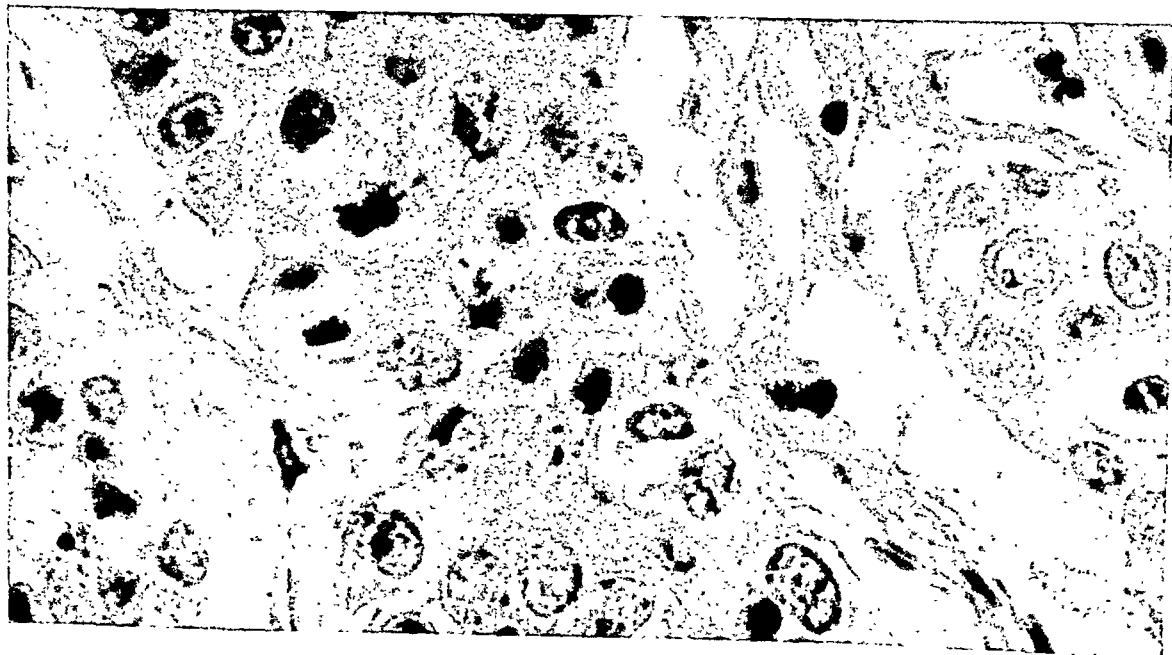


PLATE 15

FIG. 39. Stages in development of adamantoblastoma. Mouse 2. (A) Monocystic adamantoblastoma with no solid epithelial proliferations and with a minimal amount of stroma. (B) Displaced incisor tooth from whose enamel organ this tumor arose. $\times 8$.

FIG. 40. Stages in development of adamantoblastomas. Mouse 2. (A) Multicystic adamantoblastoma. (B) Small amount of inflammatory exudate in cyst. (C) Hemorrhagic cystic content. (D) Tongue. (E) Stretching and lengthening of masseter muscles by expansive growth. (F) Resorption of ramus and replacement by neoplastic tissue. (This tumor is one of bilateral growths in a single animal. Figure 39 represents the other tumor. See also Figure 6 for another multicystic adamantoblastoma.)

FIG. 41. Stages in development of adamantoblastomas. Mouse 13. Multicystic solid adamantoblastoma. (A) Cystic portions. (B) Solid epithelial areas with numerous small areas of cystic breakdown among epithelial masses and strands. (C) Enamel space surrounded at "D" by enamel organ proliferations. (E) Incisor tooth displaced lingually by tumor growth. (F) Posterior root portion of same tooth which has been displaced superiorly by tumor. (G) Oral ulceration but with no epithelial proliferation from this source. (Note thinness and lengthening of masseter muscle at periphery of tumor.) $\times 10$.

FIG. 42. Stages in development of adamantoblastomas. Mouse 51. Solid epidermoid adamantoblastoma. (A) Area of previous excision for biopsy. (B) Invasion into masseter muscles. (C) Oral ulceration with epithelial downgrowths. (D) Proliferation from enamel organ of incisor tooth. $\times 10$.

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PLATE 16

- FIG. 43. Stages in development of adamantoblastomas. Mouse 65. Multicystic epidermoid adamantoblastoma. $\times 10$.
- FIG. 44. Mural attachments to cystic linings. Mouse 9. (A) Mural proliferations from cystic lining. (B) Epithelial masses in stroma which have become severed from the cystic lining and which transform this tumor from a purely cystic to a cystic-solid growth. $\times 11$.
- FIG. 45. High-power photomicrograph of area in Figure 44. (A) Cystic lining. (B) Mural epithelial masses attached to the cystic lining. (C) Similar masses without demonstrable attachment. $\times 385$.
- FIG. 46. Sarco-adamantoblastoma. Mouse 21. (A) Sarcomatous portion of mixed tumor with giant cells at B. (C) Epithelial portion of mixed tumor. (D) Cystic space with inflammatory exudate. $\times 155$.

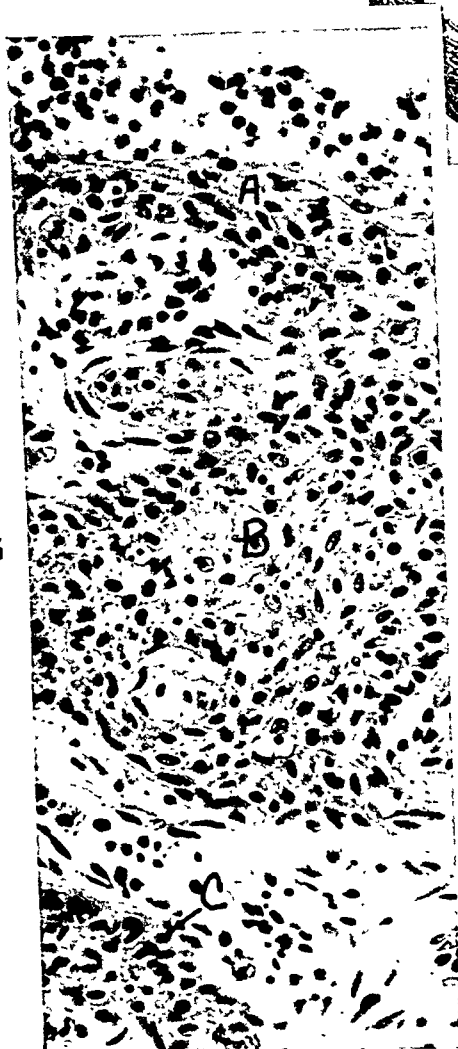


PLATE 17

- FIG. 47. Odontoma. Mouse 11. Bizarre pattern of an odontoma formed by the irregular laying down of neoplastic tooth elements. (A) Enamel space. (B) Dentin. (C) Pulp tissue. There is little similarity to a normal tooth structure although almost all tooth elements, both epidermal and mesodermal, are involved in the tumor. $\times 13$.
- FIG. 48. Odontoma. High power of portion of Figure 47. (A) Enamel space with organic matrix. (B) Dentin. (C) Pre-dentin. (D) Odontoblasts. (E) Pulp. (F) Ameloblasts. (G) Enamel organ. Note the wild, bizarre arrangement of enamel, dentin and pulp structures with no regular tooth pattern discernible. The odontoma represents a tumor of *both* enamel and dentin, *i.e.*, of both epithelium and connective tissue. $\times 145$.
- FIG. 49. Monocystic adamantoblastoma which is similar to what is known as a dentigerous cyst in man. Longitudinal section. Mouse 64. (A) Cystic tumor surrounding the enamel space (B) of incisor tooth. (C) Peridental membrane uninvolved. (D) Auxiliary cyst which appears as an individual structure but is actually a lobule of the large cyst. $\times 11$.

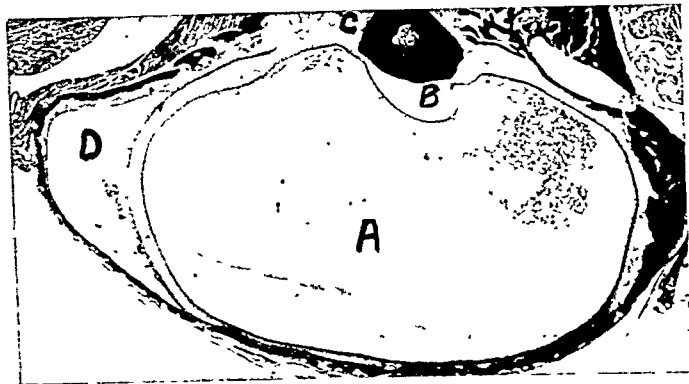
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EXPERIMENTAL THROMBOTIC BACTERIAL (STREPTOCOCCUS VIRIDANS) ENDOCARDITIS

I. ITS PRODUCTION AND INCIDENCE IN THE RABBIT *

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The primary objective of these experiments was to help resolve the problem of therapeusis in subacute bacterial endocarditis. The more rational and innocuous approach of animal experimentation appealed to us rather than direct evaluation of new expedients in human patients afflicted with the disease. It is true that countless therapeutic measures have been advanced for this disease, which alone attests to the futility of most of them.

For our purpose it is essential that the disease be reproduced consistently in a convenient laboratory animal. This initial report deals with methods and procedures adopted to achieve the greatest possible incidence of the experimental disease in rabbits.

Experimental endocarditis produced by bacteria other than *Streptococcus viridans* isolated from human cases has been reported many times.¹⁻³ There are also numerous reports of experimental endocarditis produced by traumatizing the endocardium or by the injection of particulate matter in addition to bacterial inoculations.⁴⁻⁷

Dreschfeld,⁸ in 1887, was the first investigator to reproduce the disease without first resorting to mechanical injury of the cardiac valves. Horder⁹ and Rosenow¹⁰ also produced endocardial vegetations by simply injecting intravenously cultures of *Str. viridans*. The most recent work in this direction is the splendid accomplishment of MacNeal, Spence and Wasseen,¹¹ who demonstrated that it is possible to transmit endocarditis lenta of man to the rabbit by repeated intravenous injections of large amounts of pure cultures in serum-broth.

The technic followed was an adaptation of the pattern suggested by MacNeal and his co-workers.¹¹ Strains of *Str. viridans* were obtained by blood culture from clinically typical cases of subacute bacterial endocarditis. The organisms were subplanted in meat infusion broth which was occasionally enriched with rabbit plasma. One to 6 cc. of a fresh 24-hour culture was injected daily into an ear vein of a rabbit for 6 days. After an interval of 48 hours, a blood culture was taken and the sequence then repeated. This program was continued for variable periods until repeated positive blood cultures, progressive loss in weight and the development of cardiac murmurs heralded the presence

* Received for publication, February 26, 1943.

of endocardial vegetations. Some animals died spontaneously, others were sacrificed. In some series attempts were made either to prevent or to cure the experimental disease. These results will be reported in a later communication. Necropsies were performed as soon after death as possible. Where vegetations were found, the organisms could be demonstrated histologically with ease, as well as in cultures. Mitral lesions predominated, although aortic, tricuspid and multiostial lesions were also encountered. Gross renal and splenic infarctions were observed as were the typical microscopic, embolic, renal lesions of Löhlein.¹²

The initial experiments were begun in August, 1940. For this series 31 rabbits and five strains of *Str. viridans* were employed. For these probatory experiments the organisms were grown in plain meat infu-

TABLE I

Strain	No. rabbits	No. positive	Per cent positive
M	1	1	100.0
R	6	3	50.0
S	7	1	14.0
H	5	0	0.0
A	2	1	50.0
M and R	10	5	50.0
Total	31	11	35.5

TABLE II

Strain	No. rabbits	No. positive	Per cent positive
S	7	3	42.8
H	8	8	100.0
B	6	4	66.6
Total	21	15	71.4

sion broth and only 1 to 2 cc. of the fresh 24-hour culture was injected. The results of this early experiment are shown in Table I.

For the purpose of this work the results in this series were too desultory and unpredictable. It was felt that the percentage of animals with endocarditis could be improved by stepping-up the virulence of our strains. With this in mind the H and S strains, which incidentally had given the poorer results, were passed through mice and cultured on broth enriched with rabbit plasma. In addition, the daily dose of inoculum was increased to 4 cc. Finally, a recently isolated and, presumably, more virulent strain was singled out and employed. The more helpful response is noted in the experiments summarized in Table II.

The inferences to be drawn from these experiments are that different strains of *Str. viridans* vary in their capacity to produce endocardial lesions in the rabbit, and, further, that this potentiality can be enhanced by passage of weak strains through mice, or by growth in enriched mediums, or both.

This thesis was confirmed in the next series of experiments which were begun in May, 1941. Streptococcal strains H and B, which were permitted to deteriorate by transplanting in plain meat infusion broth, were employed, as were two newly recovered strains of *Str. viridans*, F and G. The results are summarized in Table III.

Thus, endocarditis was produced in only 4 of 15 rabbits with the use of the devitalized strains H and B. On the other hand, fresh, relatively virulent strains F and G produced lesions in 8 of 11 animals.

TABLE III

Strain	No. rabbits	No. positive	Per cent positive
H	7	3	42.8
B	8	1	12.5
F	5	5	100.0
G	6	3	50.0

CONCLUSIONS

1. The rabbit is a suitable and convenient laboratory animal for the experimental production of subacute bacterial endocarditis.
2. A simple technic is outlined for the production of the disease in rabbits.
3. Different strains of *Str. viridans* vary in their ability to produce the experimental disease in the rabbit.
4. The virulence of weak strains of *Str. viridans* can be enhanced by passage through mice and by culturing on enriched mediums.
5. Subacute bacterial endocarditis was produced in from 50 to 100 per cent of rabbits in adequately controlled experiments.

We are indebted to Mr. Mortimer Russell for his technical assistance in this study.

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DESCRIPTION OF PLATE

PLATE 18

- FIG. 1. Rabbit 903. Thrombotic endocarditis of tricuspid valve. This was combined with a mitral lesion. $\times 1.4$.
- FIG. 2. Rabbit 903. Thrombotic endocarditis of mitral valve. (See Fig. 1.) $\times 1.2$.
- FIG. 3. Rabbit 16. Thrombotic endocarditis of aortic valve. $\times 1.4$.
- FIG. 4. Rabbit 631. Infarct in kidney. Heart revealed aortic endocarditis. $\times 1.6$.
- FIG. 5. Rabbit 13. Experimental thrombotic endocarditis involving the aortic valve, showing complete destruction of cusps and huge vegetation harboring clumps of streptococci. $\times 20$.



3

5

PROGRESSIVE EXPERIMENTAL ENDOCARDITIS LENTA *

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In a previous paper ¹ we considered some of the very early changes observed in the hearts of rabbits after they had received repeated large intravenous inoculations of *Streptococcus viridans*. Such animals have shown evidence of a widespread infection of the endothelial cells of the endocardium and a tendency for the infection to progress to more serious destruction in certain locations, especially on the auricular faces of the mitral and tricuspid leaflets, on the ventricular faces of the aortic cusps, on the intima of the ascending aorta and in the myocardial capillaries. When the experimental animals survive for longer periods, *i.e.*, 1 to 10 weeks after the initial inoculation, there is found abundant evidence that the original widespread infection has been overcome by the local defense mechanisms in many places, in some locations with apparently complete restitution and at other sites only at the expense of more or less serious structural alteration, while in still other localities the infectious process persists and eventually leads to local alterations and to distant complications, such that the life of the animal can no longer continue. During this progressive stage of the disease there are thus presented apparently conflicting phenomena of healing and of destruction. In the present paper we purpose to invite attention especially to the destructive tissue alterations on the valve leaflets and their relationship to the behavior of the bacterial invaders, deferring for the most part the consideration of repair and healing.

In a great majority of our experimental animals, now numbering many hundreds, the disease has progressed to death. The most conspicuous gross lesions are the vegetations on the mitral, aortic and tricuspid valve leaflets, on the mural endocardium, on the aortic intima and rarely on the pulmonary semilunar cusps. The vegetations in the rabbit are relatively larger than those ordinarily seen in the human heart. Sometimes the animals survive until the stenosing mitral mass of morbid material seems to obstruct almost completely the passage from auricle to ventricle. The finer structure of these vegetations is

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variable but essentially of the same nature as that seen in the human lesions.² In addition to the valvular vegetations, there are found also septic lesions of the kidneys and lungs, similar to those in man, enlargement of the spleen, usually without infarction, and interesting alterations in blood vessels and in the myocardium, some of which are still only imperfectly elucidated. There is considerable variation in different animals in respect to character, location and rate of development of the lesions. Nevertheless, some changes are seen especially in the early days or weeks of the infection and others are found chiefly in animals ill for a month or more.

Rabbit 4 of series 10 weighed 3600 gm. on May 10, 1939. It was inoculated intravenously with pooled culture strains of *Str. viridans* isolated from four patients: Pl, Fi, Ha and Ho. The bacteria were grown in rabbit-serum broth, sedimented by centrifugation, resuspended in saline solution, pooled and injected into the ear vein. The bacterial growth of 20 cc. of the serum broth was represented by 2 cc. of the final suspension. Rabbit 4 received 0.5 cc. of such pooled suspension daily on May 11, 12 and 13, a total of 1.5 cc. It died at 11:00 a. m. on May 15, only 4 days after the initial inoculation. At necropsy there was found a small vegetation on the tricuspid valve and a slightly larger one on the mitral valve.

A section through the mitral valve is represented by the photomicrograph, Figure 1. The original substance of the leaflet is swollen and distorted and on its auricular face there is a thick deposit of fibrin, in part so friable as to be fragmented in the section. Wandering cells are abundant in the substance of the leaflet just beneath the fibrin and collections of wandering cells are present also in some parts of the fibrin deposit itself. For the most part, however, the latter is relatively or entirely free from nucleated cells. Colonies of streptococci are abundant and irregularly distributed throughout the mass of fibrin. Some bacterial colonies are found near the substance of the leaflet proper, but not in it. The most superficial layer of fibrin also appears to be free from bacterial colonies. The colored drawings, Figures 4a, 4b and 4c, represent a narrow strip in this same section extending through the substance of the leaflet from the ventricular endothelial surface (a) to the deepest portion of the fibrin deposit on the auricular aspect, in which the deep group of bacterial colonies can be recognized in the photomicrograph (Fig. 1). The top colored strip (a) shows the ventricular surface of the leaflet, where the endothelial cells are swollen, somewhat basophilic and apparently increased in number. Beneath them, the connective tissue is edematous and has in it polymorpho-

nuclear leukocytes, some eosinophils and lymphocytes. The second colored strip (b) carries on to the right of strip a, showing the mid-portion of the leaflet proper. Here the edema is greater and the cellular infiltration somewhat less. Toward the right end of the strip there are more fragmenting leukocytes. The third strip (c) carries on to the right of strip b. Here the wandering cells have become more abundant and the infiltration with polymorphonuclear leukocytes extends almost to the necrotic auricular surface of the leaflet, where it is intimately adherent to the fibrinous vegetation, containing colonies of streptococci. There is an appreciable interval of cell-free fibrin separating the bacterial colonies from the stainable nucleated tissue cells and leukocytes. Apparently the large bacterial colonies, during the rapidly progressive stage of their growth in fibrin, are able to keep the living body cells at a distance. On the other hand the endothelial cells of the endocardium at this stage seem to have become altered so that they either fail to phagocytize the isolated cocci which are circulating in the blood or, more probably, have acquired the ability to digest and dissolve the streptococci quickly after they have been phagocytosed so that the bacteria are not found in them at this stage of the disease.

Rabbit 621, series 18, weighed 2580 gm. on November 21, 1939. It was injected intravenously with immune serum from November 21 to December 1 inclusive, 10 cc. daily except November 26, to a total of 100 cc. This serum was derived from rabbits immunized against *Str. viridans* and it possessed a high agglutination titer. Subsequent to the start of the serum injections, rabbit 621 was inoculated intravenously with a suspension of bacterial culture, *Str. viridans*, strain Cr., which had been grown 18 hours in broth, centrifugalized and suspended in physiological saline solution, the bacterial growth of 20 cc. broth culture being represented by 2 cc. of the final suspension in saline solution. The rabbit received 2 cc. of such suspension daily on November 23, 24, 25, 27, 29 and 30 and on December 1, a total of 14 cc. It died on December 2, 1939, 9 days after the initial bacterial inoculation. At necropsy there was found an irregular rough vegetation on the tricuspid valve and a rough deposit, 9 by 6 by 4 mm. in diameter, on the right mural endocardium near the right border of the heart. On the left side the mitral orifice was occupied by a vegetation measuring 8 by 6 by 6 mm. The aortic and pulmonary valves appeared negative. A gross photograph of the opened heart is shown in Figure 2.

A section passing through the mitral valve is represented by photomicrograph in Figure 3. One can recognize the deformed and thickened structure of the valve leaflet and the large, irregular and somewhat

fragmented mass of fibrin deposited on its auricular face, but also extending onto the ventricular surface of the valve and onto the ventricular wall at an area of contact. Many nucleated cells are present in this vegetation and also many colonies of streptococci. The latter appear in the photomicrograph as black spots of irregular size and outline, especially numerous near the ventricular surface of the mass. The colored drawing, Figure 5, shows a small bit of the ventricular wall where the friable vegetation is attached. Streptococci can be recognized only in the dense colonies and one searches in vain for individual cocci in the endocardial exudate, in the altered endothelium and also in the subjacent muscle which has been infiltrated by exudate.

Rabbit 822, series 26, weighed 2620 gm. on October 9, 1939. It was given intravenous injections of *Str. viridans*, strain Ep., 2 cc. of the usual type suspension daily on October 9, 10, 11, 12, 14, 15 and 21, to a total of 14 cc. Beginning on October 22, sodium sulfathiazole was given intravenously, 50 mg. per day on October 22, 23, 24, 25, 26, 28, 29, 30 and 31 and on November 1. The body weight was 2370 gm. on October 14, 2070 gm. on October 21 and 1900 gm. on October 28. The blood culture taken on October 14 was negative, that of October 21 positive and, again, that of October 28 positive. Auscultation on October 30 and again on November 1 detected abnormal heart sounds. The animal was found dead on the morning of November 2, 24 days after the initial bacterial inoculation. At necropsy there was abundant fluid in the peritoneal cavity; the heart was enlarged and the mitral ring was almost completely obstructed by massive vegetations.

A photomicrograph of a section through one of the mitral vegetations is shown in Figure 6 and the colored drawing, Figure 7, represents a small portion at the free surface of this same section. Apparently this is an example of a very malignant, actively progressive lesion on the valve leaflet. The bacterial colonies are seen extending to the free surface of the vegetation and evidently disintegrating here so as to free abundant streptococci into the circulating blood at every beat of the heart. The subjacent fibrin in this particular part of the vegetation is devoid of wandering cells and the bacterial colonies appear to be flourishing here without hindrance.

Rabbit 100, series 5, weighed 2090 gm. on February 10, 1939. It was given a series of intravenous injections of heat-killed bacterial vaccine made from strain Fi., *Str. viridans*, three times a week from February 10 to April 10 inclusive. The initial dose was $\frac{1}{2}$ billion and the last five doses were each 10 billion bacterial cells. The animal lost weight to 1950 gm. on February 20 but then gained steadily to 2610

gm. on April 10. The total bacterial cells used for this preliminary immunization amounted to 120 billion. After an interval of 10 days the intravenous inoculations of living bacterial culture were begun on April 20, employing a suspension of the same strain of bacteria in saline solution, of which 2 cc. represented the growth in 10 cc. of serum-broth medium in 18 hours. This was given as follows: 2 cc. on April 20; 4 cc. on April 21; 5 cc. on April 22, 24 and 25; and 5 cc. on May 4, 5 and 8. The total amount of inoculum was 36 cc. The animal weighed 2640 gm. on April 24, 2415 gm. on May 1 and 2450 gm. on May 8. Blood cultures taken on April 24 and 27 were positive, those taken on April 29 and May 1 were negative and the final one taken on May 8 gave positive growth. The rabbit died on May 17. At necropsy there were large vegetations on the aortic ring.

A photograph of the vegetations is shown in Figure 8 and a section through the aortic vegetation is represented by the photomicrograph in Figure 9. There is a large mass of fibrin containing abundant bacterial colonies situated on the ventricular surface of the leaflet and there is similar morbid material attached to the adjacent ventricular endocardium. The colored drawing, Figure 10, depicts a small area of the section at the free border. At this place the deeper portion consists of cell-free fibrin in which there are abundant flourishing colonies of streptococci and many vacant clefts. Over this deepest layer there is a more compact layer of fibrin containing fragmented and deformed wandering cells and apparently free from bacteria. This is overlaid by a third stratum, of recent origin, in which abundant, well preserved erythrocytes and leukocytes can be recognized in the clot. Apparently this layer had been deposited during the last hours of life. On the other hand, the layer containing the deformed leukocytes would seem to have been deposited earlier and to indicate an attempt to wall in the infected mass by fibrin into which the bacteria could not readily penetrate. The appearance suggests, therefore, a somewhat greater tendency to resist the infectious agent than that evident in rabbit 822.

Rabbit 655, series 16, weighed 2420 gm. on October 9, 1939. It was inoculated intravenously with culture strain Cr., *Str. viridans*, the daily dose representing the centrifugalized growth of 18 hours in 10 cc. serum broth, separated and suspended in 2 cc. of physiological saline solution, or multiples of this amount. At the same time rabbit serum possessing a high agglutinin titer against the streptococcus was injected intravenously. The doses are indicated in Table I. The animal died on November 7. At necropsy there were found small rounded vegetations on the mitral leaflets and a large vegetation on the aortic valve.

The gross appearance is shown in Figure 11. A photomicrograph of a section passing through the aortic valve and the ostium of a coronary artery is shown in Figure 12. The aortic leaflet is partly covered on both surfaces by a mass of relatively cell-free fibrin in which there are abundant crowded colonies of streptococci growing out to the free surface of the vegetation. On the adjacent wall of the aorta there is a large intimal plaque made up for the most part of bacterial colonies. Beneath this the media of the aorta is swollen by edema fluid and is superficially invaded by the bacterial growth. A small portion is represented in detail in the colored drawing, Figure 13. Here it seems that the bacterial colonies have been able to digest the collagen and elastin of the aortic wall so that they penetrate into it and, at the same time, to produce necrotizing substances which cause disappearance of neighboring cell nuclei and edema of the more distant tissue elements.

TABLE I
Protocol of Inoculation and Treatment of Rabbit 655

Date period 1939	Weight	Blood culture	Daily inoculum	Daily serum dose
	gm.		cc.	cc.
Oct. 9	2420			
Oct. 10			2	5
Oct. 11 to 14			4	5
Oct. 16 to 21	2500	Negative	4	5
Oct. 23	2370	Negative	4	5
Oct. 24 to 28			6	5
Oct. 30 to Nov. 4	2250	Negative	6	5
Nov. 6	2120	Positive	None	None
Total amounts			112	115

From the study of the progressive types of vegetations on the cardiac valves of the rabbits, only a few of which can be illustrated and described, it is possible to form a fairly definite idea of the general course of events at these sites. The initial bacterial invasion of the blood stream is followed by phagocytosis of the streptococci, a process in which the endothelial cells lining the blood vascular channels play a prominent rôle. The biological factors which favor or inhibit the phenomenon of phagocytosis at a particular site or at a particular time are only imperfectly understood. The phenomenon is by no means limited to the heart, for it seems that the intimal lining of vascular channels in the liver, spleen and lungs is even more actively concerned in this phagocytosis. In the heart itself the blood vessels of the myocardium are seriously involved in the removal of the streptococci. However, our immediate present attention is directed to the participation of the endocardium and especially to that of the valve leaflets.

Most of the streptococci appear to be killed and digested by the phagocytic endothelial cells which become somewhat swollen and lose their normal, relatively thin, flat form to assume a more rounded contour. They are in part destroyed also, but in some places they are stimulated to multiply by mitotic cell division. If complete destruction of the microbes is accomplished for each succeeding invasion of the blood, then the animal escapes development of bacterial vegetations. This has evidently taken place in a considerable number of the experimental rabbits, even after repeated inoculations. In them the restitution of the endothelium may be so complete that evidence of injury may not be recognized. On the other hand, the matter turns out otherwise when the active virulence of the bacteria is relatively great and the resistance of the animal naturally weak or lowered by other disease such as severe coccidiosis. In such, the streptococcal infection may overwhelm the host in the early bacteremic stage before local gross vegetations arise. Between these two extremes there is produced a less rapidly fatal infection in which the vegetations characteristic of bacterial endocarditis are conspicuous features. The mitral valve is the most common location and the favorite area is along the line of contact where the leaflets are pressed against each other during ventricular systole, that is, on the auricular faces near the free margins. Corresponding relatively vulnerable areas may be recognized on other valves.

At such a susceptible site the initial infection of the endothelial cells is followed by their swelling and the accumulation of edema fluid in the stroma beneath them. The injury to the endothelial cells may cause their separation so as to expose the subjacent stroma or it may serve merely to release sufficient thromboplastic elements to bring about a deposit of platelets and fibrin on the surface without loss of the endothelial coat. In either event the fibrin deposit, once started, tends to increase. In its meshes are included streptococci which find in it a favorable medium for the production of large bacterial colonies. One may well agree with the usual statement that *Str. viridans* is an organism of low virulence, but nevertheless when these large colonies are growing rapidly in the fibrin they produce substances which are ordinarily able to keep at a distance any living body cells and these bacterial products bring about a remarkable hydrophilic change in the neighboring connective tissues, manifest by edematous swelling and fragmentation of their structure in addition to the accumulation of various wandering cells and the proliferation of the fixed elements. The valve proper thus becomes greatly thickened. The fibrinous deposit on its surface continues to add more and more fibrin from the blood stream at its free

surface while the streptococci multiply in its substance. Red and white cells may be included, coming from the blood stream. The free surface of such a progressive vegetation is jagged, irregular and easily broken so that fragments of the fibrin and bacteria from the actively growing colonies near to and on the free surface may be set free into the general circulation.

The underlying stroma of the original leaflet may undergo partial necrosis or it may respond by proliferation of its elements. In most lesions of longer standing both phenomena are represented by necrosis at one place and fibroblastic proliferation at another. Remarkable deformity and intermingling of infected fibrin, necrotic and suppurating stroma, proliferating fibrous tissue and proliferating endothelium may thus be produced, resulting in a confused and confusing arrangement similar to that often seen in the human lesions of longer duration. The inflammatory changes in the living stroma may be associated with the formation of blood spaces lined by endothelium or of genuine blood capillaries, elements which, in the human lesions, have supplied a topic for controversy.

In some rabbits, because of greater resistance of the animal or relatively lesser virulence of the infection, the necrotizing effect is diminished and the reparative exudation and proliferation relatively enhanced. Sometimes the new layer of fibrin is relatively free from bacteria for a space and then again heavily infected on or near the surface so that the vegetation presents a succession of layers. In such a vegetation the deeper colonies are often made up of minute, poorly staining cocci, apparently relatively suppressed. Over them the layer of bacteria-free fibrin indicates restraint of bacterial growth in this layer. Then on top of this there may be a fresh deposit of fibrin rich in flourishing bacterial colonies in which the individual cocci are relatively large and stain very well. Such lamination evidently indicates a period of relative resistance followed by a recidive of infectious activity. The more or less successful opposition to the microbes seems to depend especially upon unseen soluble elements in the blood which tend to hamper rapid bacterial growth, and the most conspicuous early effect of this is manifested by the deposit of a bacteria-free coat of fibrin on the free surface of the vegetation so as to bury the bacterial colonies and keep them from the circulating blood. Over this layer of bacteria-free fibrin the endothelial cells of the adjacent endocardium may extend to form a smooth protective coat, and into the fibrin may grow proliferating fibroblasts, much as such cells grow into the fibrin of a tissue culture *in vitro*. These changes suggest the nature of a possible heal-

ing process and will require renewed consideration when we discuss the arrested and healing stages of the experimental disease. They are, however, seen here and there in some animals in which the disease progresses actively to a fatal termination. Even when the infecting bacterium seems to have been brought under restraint, the structural damage already inflicted may result in lethal dysfunction.

The aortic valve, which is the second most frequent site of large vegetations, shows changes essentially similar to those seen on the mitral leaflets. Here the vegetation appears to start by preference on the ventricular surface of the leaflet, again at the line subjected to pressure against the endothelium of a fellow cusp. The progress of the aortic vegetation is like that of the mitral but there is here apparently a greater tendency for bacterial growth to extend onto the adjacent aortic intima and into the coronary arteries and also a greater tendency for gross fragments of vegetations to escape into the aortic blood stream.

On the tricuspid leaflets the vegetations are usually smaller, often multiple and separate and they tend to be smoother and less friable than those of the left heart. Organizing fibrosis and covering by smooth endothelium are more frequently seen here, in our experience. Apparently the less violent pressure changes favor the healing tendency but one cannot be certain whether the concentration of carbon dioxide and deficiency of oxygen play any part. Healing tricuspid vegetations may be found in the same heart along with violently progressive lesions on the mitral and aortic leaflets.

Vegetations on the tendinous cords and papillary muscles occur more frequently in the right heart but they are more destructive when they are found in the left ventricle, where the chordae tendinae are severed not infrequently. In the right ventricle, on the other hand, one often finds evidence of healing in the vegetations on the tendinous cords.

Changes in the mural endocardium are of special interest. The initial diffuse infection of this endothelial layer is rarely recognized and in general it seems to be of relatively brief duration in the rabbit. Apparently this diffuse infection is rapidly overcome by the intracellular digestion of the phagocytosed streptococci, without recognizable permanent morphological change in the endothelium. However, its functional relation to the bacteria appears to have been altered as a result of this experience so that subsequently the bacteria either are not phagocytosed or if phagocytosed are rapidly annihilated. At any rate one searches in vain for microscopical evidence of general bacterial infection of the mural endothelium of animals dying during the later weeks of the

disease. In some locations the early destruction of the phagocytosed bacteria is associated with endothelial and subendothelial injury, probably because the disintegrating bacterial cells liberate too much toxic material and some of the microbes escape destruction and are able to multiply in the injured endothelial cells and in the fibrin deposited over them. The structural change may include edematous swelling and fragmentation of subjacent connective tissue and heart muscle fibers, along with accumulation of wandering cells even though, at the time, streptococci have disappeared or have become so few that they escape microscopical detection. In other instances, more serious local alteration permits luxuriant proliferation of the bacteria in the superficial layers of necrotic tissue and in the local fibrin deposit, giving rise to a mural vegetation by a mechanism much the same as that operating on the valve leaflets. The mural lesions are subjected to less physical strain and trauma and they show greater tendency toward arrest and healing.

The changes in the coronary arteries and veins, and in the myocardial capillaries and in the myocardium proper seem worthy of separate discussion. Alterations in the aorta and in other blood vessels as well as the changes observed in the kidney, spleen, liver and lung can receive only passing mention. Their study in comparison with lesions observed in man appears to offer important possibilities.

SUMMARY

1. By repeated intravenous injection into rabbits of large doses of living streptococci derived from the blood of patients afflicted with endocarditis lenta it has been possible to cause, in a large proportion of these animals, a fatal disease resembling in its clinical course and anatomical alterations the disease of man.
2. The streptococci are phagocytosed by the endothelial cells in general and are evidently effectively disposed of by these cells, for the most part. They may, however, succeed in destroying the endothelial cells in certain places, especially on the valve leaflets where these cells are subjected to contact pressure when the valve is closed.
3. Serious local injury of endothelium results in a local deposit of fibrin and in this the streptococci tend to flourish to induce further toxic injury to the underlying structure of the leaflet and more deposition of fibrin from the blood.
4. The fluid blood may exercise a restraining influence and may prevent the bacterial colonies from growing in the outermost layers of the vegetation. On the other hand, this restraint may fail and the streptococci then grow out in abundance to the free surface and escape into the circulating blood.

5. Evidence of a period of relative restraint has been observed in some of the rabbits, a period succeeded by further rapid progress of the disease process on the valve.

6. The changes which tend toward healing of the valve lesions, the changes in blood vessels and in the myocardium and the lesions in other organs and tissues require further study.

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3. Brown, J. H., and Brenn, L. A method for the differential staining of Gram-positive and Gram-negative bacteria in tissue sections. *Bull. Johns Hopkins Hosp.*, 1931, 48, 69-73.

[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 19

FIG. 1. Photomicrograph of section through mitral valve of rabbit 4, series 10, which died 4 days after initial inoculation with *Streptococcus viridans*. Hematoxylin and eosin stain. The swollen and distorted valve leaflet is covered on its auricular surface by a mass of friable fibrin in which there are numerous colonies of streptococci and some large collections of wandering cells. The narrow strip through the valve leaflet is shown in detail in Figures 4a, 4b and 4c.

FIG. 2. Photograph of the opened heart of rabbit 621, series 18, which died 9 days after initial inoculation with *Streptococcus viridans*. In the right ventricle there are several vegetations which are rather smooth and white and in part located on the ventricular wall. On the left side the mitral ring is nearly filled with rough, partly excavated and discolored vegetations.

FIG. 3. Photomicrograph of section through mitral vegetation of rabbit 621, stained by the method of Brown and Brenn.³ Both auricular and ventricular faces of the valve leaflet are covered by friable vegetations which contain abundant streptococci, especially in the portion on the ventricular surface. The adjacent mural endocardium of the ventricle has become infected, apparently by contact with the vegetation on the leaflet. A small area of this invaded mural endocardium is shown in more detail in Figure 5.



3



PLATE 20

- FIG. 4a. The ventricular third of a narrow strip through the valve leaflet proper. At the left end are swollen endothelial cells of the ventricular surface of the leaflet.
- FIG. 4b. The succeeding middle portion of the same narrow strip. In this part there is more edema, and fewer wandering cells are present.
- FIG. 4c. The succeeding portion of the same narrow strip extending through the leaflet proper to include a small bit of the deepest part of the fibrinous vegetation deposited on its auricular surface. Wandering cells become very abundant as one approaches the infected vegetation but they remain at a respectful distance from the colonies of streptococci in the fibrin. The endothelial cells of the auricular surface of the valve have been destroyed. The three drawings overlap slightly at their junction lines to permit orientation.

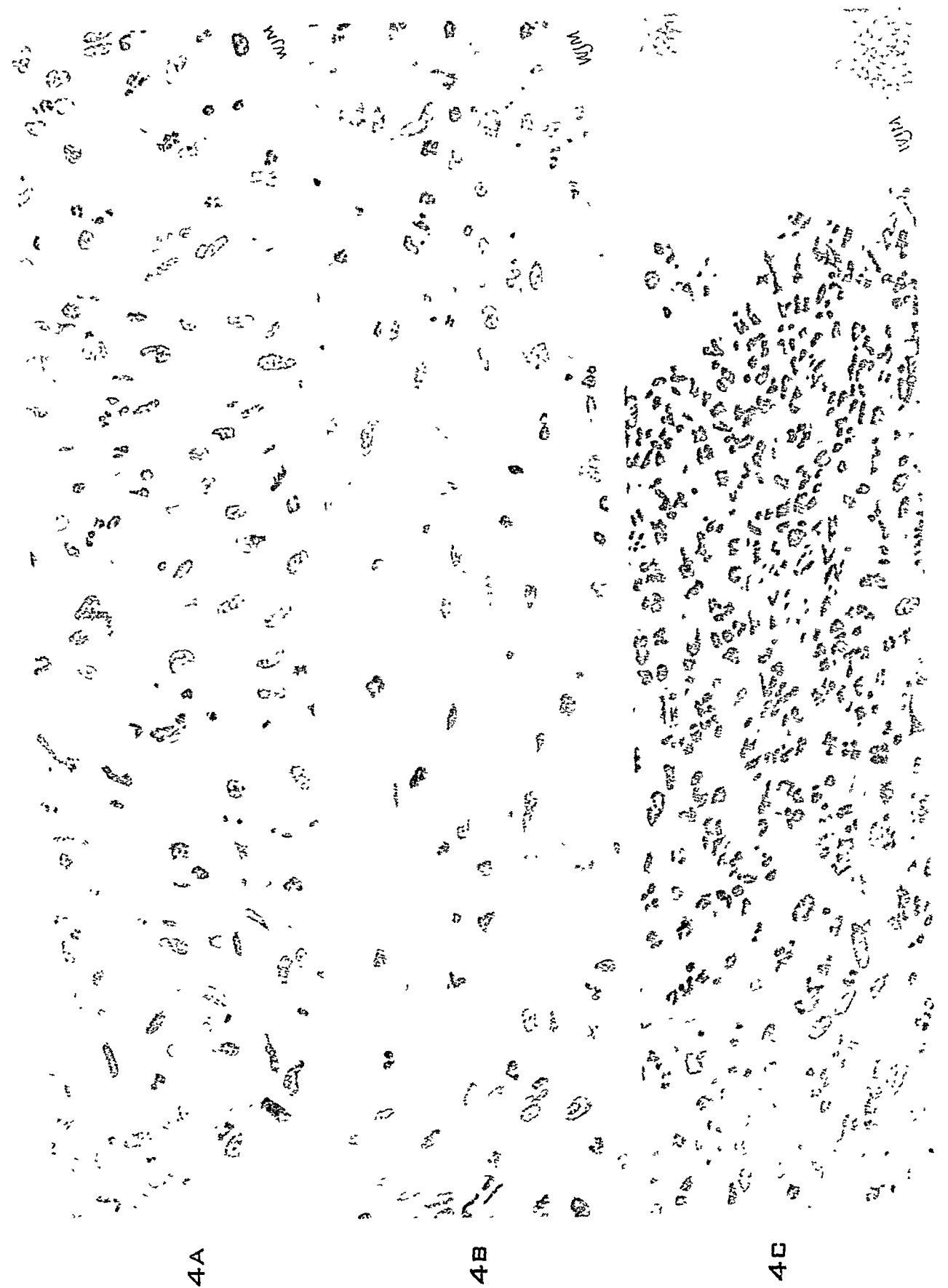


PLATE 21

FIG. 5. A small portion of the ventricular mural lesion at the location indicated on Figure 3. The muscle bundles are separated by edema and are, to some extent, infiltrated by wandering cells. The endothelial lining has been largely replaced by fibrinous deposit containing abundant, partly fragmented, wandering cells. The streptococci are recognized only in the rather large, compact colonies lying in the fibrinous deposit.



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PLATE 22

FIG. 6. Photomicrograph of section through a mitral vegetation of rabbit 822, series. 26, which died 24 days after the initial inoculation with *Streptococcus viridans*. The swollen and deformed leaflet is largely covered with vacuolated fibrinous deposit, in which there are large collections of nucleated wandering cells, appearing as very dark areas in the illustration, and also very abundant colonies of streptococci, appearing less dark, irregularly distributed through the fibrin. A small area on the free ventricular surface of the vegetation is shown in more detail in Figure 7. Hematoxylin and eosin stain.

FIG. 7. A small superficial portion of the vegetation shown in Figure 6. Here the substance consists of fibrin and abundant colonies of streptococci without any recognizable nucleated cells. The bacterial colonies extend to the free surface so as to permit easy escape of the streptococci into the circulating blood. A small amount of blood is held in a shallow depression near the right side of the upper border of the figure.

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PLATE 23

FIG. 8. Photograph of the opened heart of rabbit 100, series 5, which died 27 days after the initial inoculation with *Streptococcus viridans*. Here the mitral valve is not involved and the aortic ring is filled with rough, partly excavated vegetations.

FIG. 9. Photomicrograph of a torn and wrinkled section through the aortic valve of rabbit 100. The leaflet is hardly recognizable. In the fibrin there are abundant bacterial colonies, which are for the most part in the interior of the mass. Hematoxylin and eosin stain. A small portion at the free surface is shown in more detail in Figure 10.

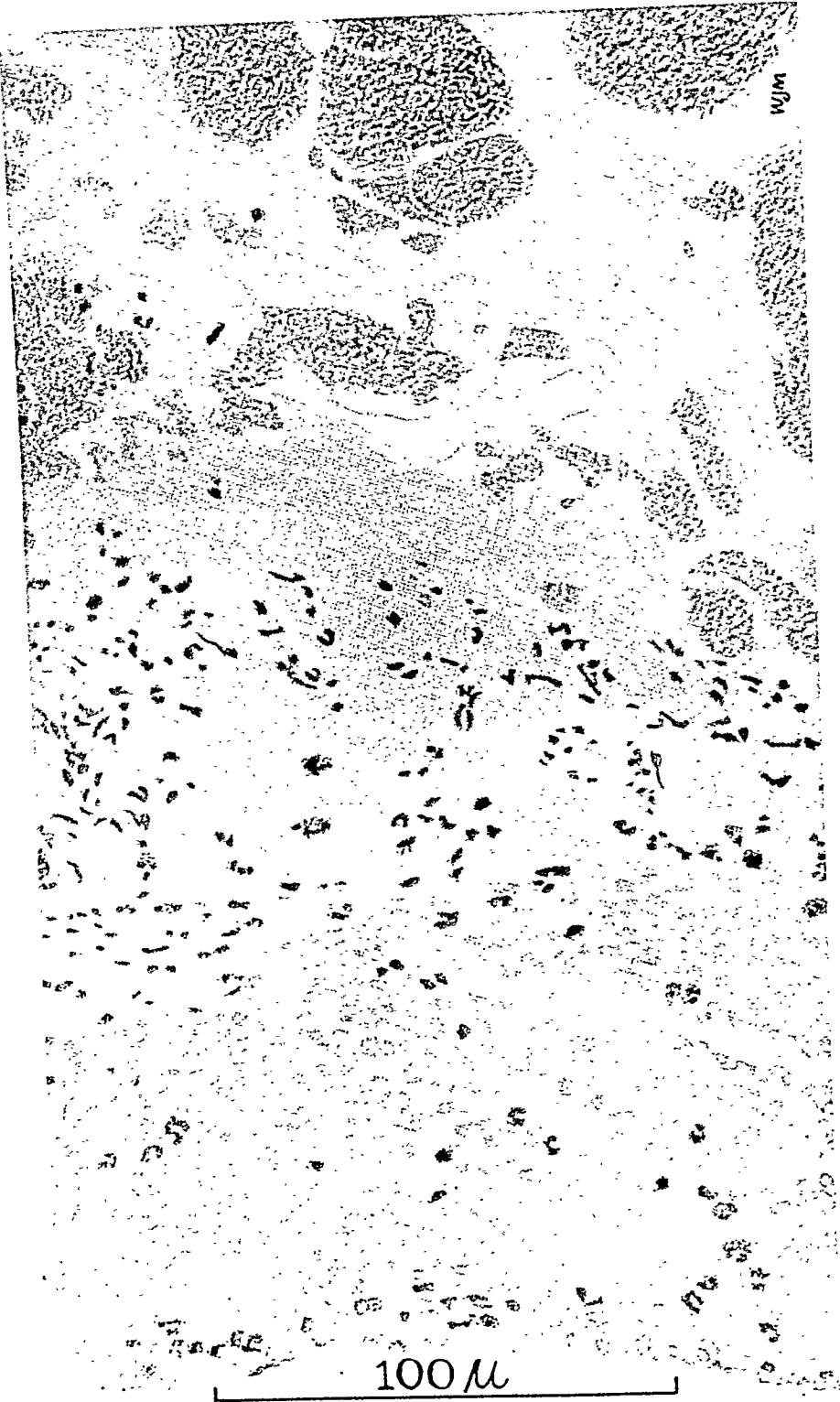


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PLATE 24

FIG. 10. A small superficial portion of the vegetation shown in Figure 9. In the deepest portion at the right the substance consists of cell-free fibrin and large bacterial colonies. Next to this there is a transition zone in which the bacterial colonies and nucleated wandering cells are closely associated, followed to the left by a zone of fibrin and fragmenting leukocytes without recognizable bacteria. Lying on this is more recent clot in which the blood corpuscles are well preserved.



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PLATE 25

FIG. 11. Photograph of the opened heart of rabbit 655, series 16, which died 28 days after the initial inoculation with *Streptococcus viridans*. There are small, smooth, white vegetations on the mitral valve leaflets and the aortic ring is filled with large, partly excavated and discolored masses.

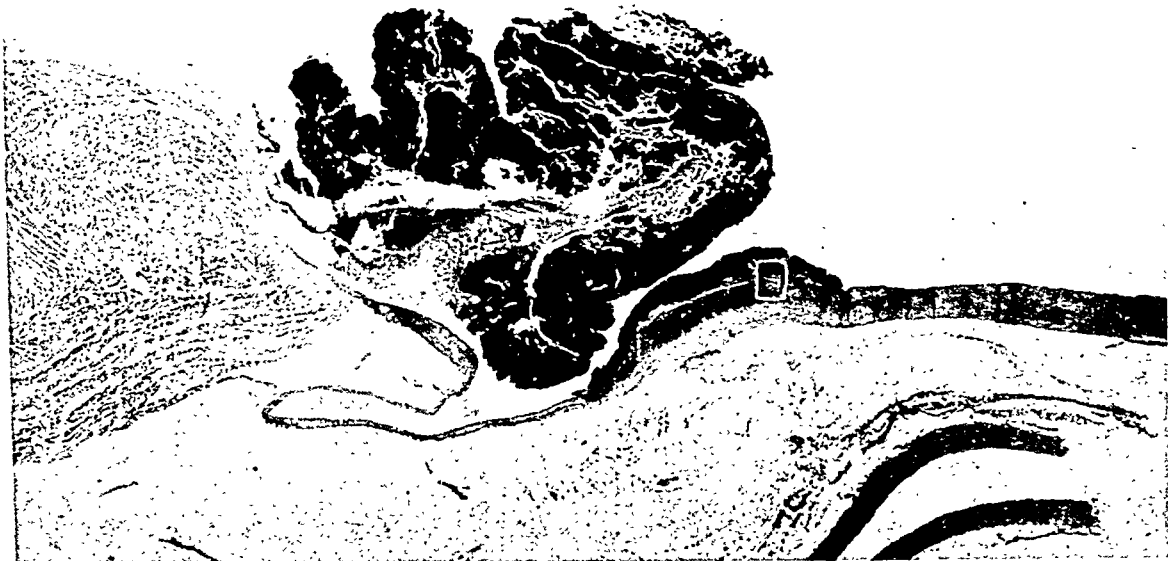
FIG. 12. Photomicrograph of a section through the aortic valve of rabbit 655, stained by the method of Brown and Brenn.³ The leaflet is covered on both surfaces by the fibrinous vegetation with closely crowded colonies of streptococci presenting everywhere on the free surface. The bacterial colonies also form a thick layer on the adjacent aortic intima along which they approach the entrance to a coronary artery. The underlying media of the aorta is somewhat swollen by edema.

FIG. 13. Drawing of a small portion of the aortic wall in relation to the massive colonies of streptococci at the point indicated in Figure 12. Here the bacterial colonies appear to invade and actually to replace the superficial elastic lamellae of the aortic wall and to cause disappearance of the nuclei in their immediate vicinity. Farther from the bacterial colonies the elastic lamellae are fragmented by edema and invaded by wandering cells. However, a deep invasion by the bacteria has been prevented.

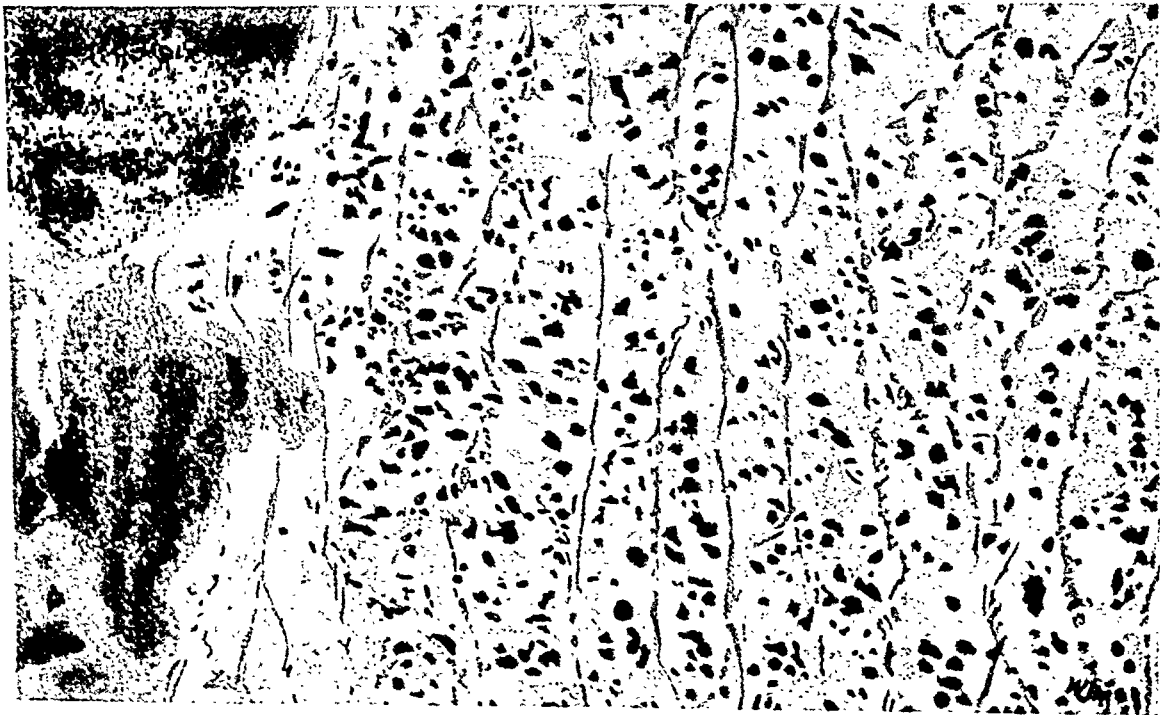
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ACUTE GENERALIZED MILIARY TUBERCULOSIS *

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Since the first description of acute generalized miliary tuberculosis by Bayle¹ (1810) there has been controversy concerning the pathogenesis of this disease. The main question has been whether the generalized dissemination of foci throughout the various organs of the body originated from a softened caseous focus (Buhl²), a vascular focus (Weigert³⁻⁷), or from within the thoracic duct.

A critical review of the literature leaves the impression that the rôle of active extrapulmonary tuberculous processes in the production of the dissemination has been underestimated and too much stress laid upon the search for vascular foci.

This study has been undertaken in order to review my cases of acute generalized miliary tuberculosis and, in the light of advanced knowledge of tuberculosis, to correlate the pathogenesis, pathology and clinical findings.

MATERIAL

In 1656 consecutive autopsies on tuberculous persons, performed in a period of 8½ years, there were 297 cases (17.9 per cent) of acute generalized miliary tuberculosis. One hundred and ninety-one of the 297 cases showed varying degrees of chronic pulmonary tuberculosis in combination with the miliary dissemination; in 106 cases a generalized miliary seeding existed alone. Orth,⁸ who found that more than half of his 30 cases of acute generalized miliary tuberculosis were associated with chronic pulmonary tuberculosis, is the only writer with whose findings my own coincide. Beginning with Weigert,³ all other authors who discussed this relationship indicated their convictions that the presence of chronic pulmonary tuberculosis excludes the development of acute miliary tuberculosis. This "Ausschliessungsverhältnis" that the more extensive the chronic pulmonary tuberculosis the less the chance for the development of an acute miliary tuberculosis, has been accepted by Schmincke,⁹ Huebschmann,¹⁰ Liebermeister,¹¹ Schürhoff,¹² Schürmann,¹³ Grethmann¹⁴ and Pagel.^{15,16}

I feel that the discrepancy between these findings and my own, results from the fact that these authors have interpreted the miliary foci found in lungs in conjunction with chronic pulmonary tuberculosis as representing bronchogenic spread from these chronic pulmonary lesions and have interpreted the miliary foci in the other organs as

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terminal hematogenous disseminations from the lungs. I feel that they have failed to recognize the combined picture.

GENERAL CONSIDERATIONS

There are a number of striking differences between the group of acute generalized military tuberculosis and the one in which this condition is combined with chronic pulmonary tuberculosis.

Age. From Table I it may be seen that in both groups the greatest number of cases is observed in the age period between 20 and 39 years. This does not agree with Grethmann¹⁴ who has reported that youth and the older ages are chiefly involved, with the middle ages relatively free of military tuberculosis. Nor does it agree with Huebschmann¹⁰

TABLE I
Age Distribution

	Birth to 10 yrs.	11-19	20-29	30-39	40-49	50-59	60-69	Over 70
Acute generalized military tuberculosis	21	10	30	26	11	4	4	0
Acute generalized military tuberculosis and chronic pulmonary tuberculosis	11	10	46	48	35	30	10	1

and Hartwich¹⁷ who emphasized the preponderance of acute generalized military tuberculosis in the first 2 decades. There is an interesting contrast in the early and late age distribution in both groups. There were 31 patients (29.2 per cent) who were less than 20 years of age in the series of uncombined acute generalized military tuberculosis and only 19 patients (17.9 per cent) who were older than 40 years. In the cases of acute generalized military tuberculosis combined with chronic pulmonary tuberculosis, on the other hand, there were 21 individuals (10.9 per cent) who were less than 20 years of age, whereas 76 (39.8 per cent) were more than 40 years of age.

This interesting contrast may in part be related to the source of the military tuberculosis. My studies have revealed that bone tuberculosis occurs chiefly in the younger age groups while the preponderance of male genital and urinary tuberculosis occurs in the older age groups. Bone tuberculosis was found in 48 of the 106 cases of acute generalized military tuberculosis; urogenital tuberculosis was found in 114 of the 191 cases of acute military tuberculosis combined with chronic pulmonary tuberculosis.

Color. In the 106 cases of uncombined acute generalized military tuberculosis 72 (67.9 per cent) were negroes, while 34 (32.1 per cent) were white. One hundred and twenty-two (63.9 per cent) of the 191

individuals showing acute generalized miliary tuberculosis combined with chronic pulmonary tuberculosis were white, while 67 (35.1 per cent) were negro and 2 (1 per cent) were of the yellow race.

Sex. An almost parallel distribution in respect to sex is present in the two groups. In the cases of uncombined acute generalized miliary tuberculosis, 73 (68.9 per cent) were males, while 33 (31.1 per cent) were females. In the other group, 147 (76.9 per cent) were males and 44 (23.1 per cent) were females.

PATHOGENESIS

Most of the discussion has centered upon the source of the hematogenous dissemination. Laënnec¹⁸ (1810) was the first to point out that older soft caseous foci could lead to extensive dissemination throughout other organs. Buhl,² carrying his teachings farther, stated that in the majority of the cases of acute generalized miliary tuberculosis there were older caseous foci in the body. He suggested the resorption of the "specific substance" into the blood stream.

Huguenin¹⁹ who shared Buhl's² view believed that the caseous mass could either erode and enter a small vein, or invade the lymphatics.

Weigert,⁷ on the other hand, stated that, since this caseous focus is frequently not found, its occasional presence in cases of acute miliary tuberculosis is not sufficient evidence for belief in it as the source of the dissemination. He pointed to the infrequent occurrence of acute generalized miliary tuberculosis in conjunction with well developed phthisis. Since, he reasoned, in phthisis there are caseous processes and softened foci as well, and since these are apparently 'insufficient for the development of acute miliary tuberculosis, there must be other factors which allow the entry of masses of tubercle bacilli into the blood stream. In 1879 Weigert⁶ observed a case of acute generalized miliary tuberculosis wherein a large caseous lymph node extended into the right innominate vein. In subsequent studies he found other venous tubercles in cases of acute generalized miliary tuberculosis. Accordingly, Weigert³⁻⁶ contended that the vascular tubercle progresses from a tuberculous focus, which extends to the vessel's wall and after destroying its intima, ruptures into the blood stream. This focus is often referred to as the "Weigert" tubercle in spite of the fact that in one study he found vascular foci in only 50 per cent of the cases and in another in 70.8 per cent. This view of the vascular focus has been accepted by Pagel,^{16, 20} Hartwich,¹⁷ Schmorl,²¹ Sigg,²² Silbergleit,²³ Baar,²⁴ Dittrich,²⁵ Herxheimer,²⁶ Schwarz²⁷ and Berghammer.²⁸

Benda,²⁹⁻³¹ likewise, believed that the vascular focus was responsible for acute generalized miliary tuberculosis. However, he considered that

the ulceration of a solitary metastasis within the intima rather than the erosion of the vessel wall by an extravascular focus was the source of the dissemination.

Ponfick³² (1877) found that in the majority of his cases of acute generalized miliary tuberculosis he could demonstrate small tubercle-like nodules within the intima of the thoracic duct. It was his opinion that the tubercles in the thoracic duct were the result of the original hematogenous dissemination. Subsequently Schürhoff¹² and Grethmann,¹⁴ in reviewing Ponfick's studies, stated that Ponfick did not recognize the tuberculosis of the thoracic duct as being primary and the generalized tuberculosis as being secondary.

Wild,³³ arguing against the views of Weigert, stated that there are too many cases (30 to 50 per cent) in which a focus cannot be found in the vein or thoracic duct. It was this author's opinion that small numbers of tubercle bacilli enter the blood stream from an active tuberculous process in the body (skeleton, urinary system, or other organ) and that the bacilli multiply in the blood stream due to certain favorable factors such as increasing virulence of the organism and special dispositional factors of the host. Ribbert^{34,35} shared Wild's views.

Huebschmann^{10,36,37} rejected Weigert's views and stated that it is frequently impossible to isolate the source of the tubercle bacilli despite diligent search. He stipulated two factors leading to the generalization. The mechanical factor of a tubercle bacillus bacteremia (based on the findings of Loewenstein³⁸ and Liebermeister³⁹) may be said to exist in all forms of tuberculosis. The dispositional factor depends upon (a) the specific component or lack of disseminated resistance in the body; and (b) the nonspecific component, or the unrelated metabolic and infectious processes of the host.

In a later study Loeschcke⁴⁰ (1931) postulated the development of acute generalized miliary tuberculosis as the result of a direct communication between a caseous focus and the blood stream without intermediate tubercle formation. Such a caseous focus, he pointed out, must contain large numbers of organisms, and through softening and liquefaction bacilli are released into the general circulation. Following this evacuation, blood enters the focus and can be readily detected microscopically. In a study of his cases of acute miliary tuberculosis which developed just before death he found grossly visible bleeding at the site of rupture with great regularity. The caseous focus which ruptured into the blood stream was usually a lymph node, but it was not infrequent to find it in the skeletal system, prostate, testis, or adrenals.

The findings of Loeschcke^{40, 42} were subsequently substantiated by Minguez.⁴¹

A study of my own material does not allow me to accept any of the views of pathogenesis which are based on the assumption of the rupture of a tuberculous focus into the blood stream. It is my opinion that the development of acute generalized miliary tuberculosis is the result of the drainage of tubercle bacilli from an active extrapulmonary tuberculous focus (skeletal system, urogenital system, serous surfaces) or a primary focus (usually progressive) into the lymphatic system. This in turn empties into the venous system (through the well known lymphovenous routes).

It is interesting to note that Buhl² and Ponfick³² alone have stated that the development of a generalized miliary tuberculosis may be the result of lymphatic drainage from a caseous focus.

The presence of an acute tuberculous process in one or more organ systems in every one of my cases of acute generalized miliary tuberculosis contradicts Huebschmann¹⁰ whose observations led him to state that the two only occasionally occur together, and that there was probably an "excluding state" between the two conditions. Pagel¹⁵ and Baar,²⁴ on the other hand, were not impressed by these "excluding" conditions, while Reisner⁴³ stated that the opposite seems to be the case.

It has been repeatedly stated that isolated organ-tuberculosis (third stage tuberculosis of Ranke, postprimary tuberculosis), in contrast to primary tuberculosis, is characterized by the absence of gross caseation of the lymph nodes. Although this is observed in the majority of cases of chronic pulmonary tuberculosis, the same may not be said of tuberculous involvement of other organ systems. It has been my repeated observation from autopsy material that progressive tuberculous involvement of the skeletal, urinary and genital systems is almost invariably characterized by caseous tuberculosis of the regional lymph nodes. The regional lymph nodes are also enlarged and caseous when there is a caseous process of the pleura, peritoneum and pericardium, and when there is extensive and deep-seated ulceration of the gastrointestinal tract. Unlike the primary complex the caseous involvement of the regional lymph nodes does not occur at the onset but usually develops in the later stages of the process. The enlargement and caseation of the lymph nodes is often not limited to the regional glands but may involve the neighboring chains.

The lymph node involvement indicates extensive lymphatic drainage of tubercle bacilli from the neighboring organ-tuberculosis, a phenomenon similar to that observed in any infection. This migration of

tubercle bacilli into the lymph nodes has been demonstrated by bacterial stains. The tubercle bacilli are carried in the lymph to the venous circulation and a generalized blood stream dissemination takes place with the development of miliary foci in the various organs of the body. Two important factors must be clarified in the consideration of a dissemination occurring in this manner: (1) caseation of regional lymph nodes does not necessarily mean that a blood stream dissemination will develop in every instance, just as it does not always develop from a pyogenic infection. The caseous process may be, and probably frequently is, walled-off with no resultant hematogenous dissemination. (2) After invasion of the blood stream takes place, the caseous involvement of the lymph nodes may become circumscribed by fibrous tissue. Repetition of the hematogenous dissemination is thus avoided and the hematogenous foci may undergo healing changes. Ample proof of this is seen at autopsy. It was observed most frequently in children in whom the generalization developed secondarily to a primary complex. These patients showed the caseous lymph nodes to contain calcium and to be encircled by a hyalinized connective tissue capsule; the tubercles in the various organs showed evidence of far advanced healing. Death, in these cases, was occasionally the result of tuberculous meningitis which developed from the generalization, but more often this cause was not related to tuberculosis.

Unlike the "Weigert tubercle," vascular perforation, or thoracic duct focus, the caseous lymph node is always present when there is a generalized miliary dissemination. It is difficult to imagine how caseous lymph nodes, laden as they are with tubercle bacilli, could exist without sooner or later pouring their contents into the general circulation via the efferent ducts.

Lymphatic drainage with subsequent hematogenous dissemination is observed in cases of chronic pulmonary tuberculosis (with or without gastrointestinal tuberculosis). The dissemination occurs most frequently into the spleen and kidney (liver is excluded because of possible portal drainage from gastrointestinal tuberculosis), but sometimes also into the adrenals and other organs including the brain. This hematogenous dissemination was observed in 33.2 per cent of the cases showing chronic pulmonary tuberculosis without associated extrapulmonary foci. In most instances caseous foci could be demonstrated within the tracheobronchial lymph nodes only on microscopic examination, but in some, particularly the more acute cases, the lymph nodes were grossly caseous. The hematogenous foci were more numerous and more widely disseminated in the individuals in whom the lymph nodes were grossly caseous.

Further propagation of the hematogenous dissemination occurs through the development of ulcerative tuberculous foci in the pulmonary veins. These foci develop in the walls of the veins (from within or without) in the course of the original seedings in the lungs. They undergo ulceration and the caseous contents laden with tubercle bacilli are carried to the left side of the heart and thence into the greater circulation.

PATHOLOGY

General Distribution

A true evaluation of the question of general distribution is beset by a number of difficulties. Whereas the lung readily lends itself to the gross identification of miliary tubercles, other organs are less productive on simple inspection. Easy recognition is of considerable importance, particularly when the dissemination is not extensive, since one millimeter foci may so readily be overlooked in routine examinations. In these instances, successful gross examination would be of immeasurable value. This is best exemplified in the kidney where division into 2 or 3 mm. slices will frequently reveal the presence of miliary tubercles overlooked in the routine examination. Such meticulous examination is of no aid in the heart, adrenals, pancreas, or thyroid gland because in these organs such foci are not recognizable on gross examination. A true incidence therefore, of the distribution within these organs can be ascertained only by serial section, a physically impossible task. The brain was removed for examination in only a small number of cases.

When the dissemination is extensive routine microscopic examination will reveal miliary tubercles in almost all parenchymatous organs.

Miliary foci were found in the lungs and spleen in all instances; in the kidney in 205 cases (69.0 per cent), in the adrenals in 84 cases (28.3 per cent), in the brain in 31 cases (10.4 per cent), in the pancreas in 14 cases (4.7 per cent), and in the thyroid in 10 cases (3.4 per cent).

Lungs

Clinical and Anatomic Correlations. The gross appearance, histologic characteristics and serial roentgenograms must all be considered in determining the development and ultimate fate of the miliary tubercle. Since all of the 297 patients in my series were in our institution, suffering from some form of extrapulmonary tuberculosis, an excellent opportunity was afforded to study the development and ultimate fate of the miliary dissemination. In this correlation only those cases were considered in which the lungs were clear before the hematogenous dissemination. The only proof of pulmonary seeding is the roentgeno-

gram; clinical signs and symptoms must be verified by x-ray examination. Huebschmann and Arnold,⁴⁴ in attempting to arrive at a classification of hematogenous seeding based on clinical signs and symptoms, came to the conclusion that there is a definite relationship between the clinical and anatomic pictures of generalized miliary tuberculosis; this, in spite of the fact that a number of their clinical observations did not coincide with the anatomic findings. Grethmann¹⁴ and Pagel¹⁵ emphasized the difficulty of correlating the age of the disease with the clinical data. None of the authors mentioned roentgenographic studies as correlation. I feel that this is a vital omission.

Some of the patients in my series whose earlier roentgenograms showed either clear fields or at most a few scattered foci in the apical portions, and who were observed over a period of months, developed diffuse disseminations in the lungs. Yet gross and microscopic studies revealed both recent and very old foci. The answer to this discrepancy lies in the fact that sufficiently early roentgenographic observations were not available. Occasionally, however, I have had the opportunity of observing the following course: a patient with some form of extrapulmonary tuberculosis has a roentgenogram which clearly demonstrates a diffuse miliary lung field dissemination. Subsequent studies then demonstrate progressive clearing from the caudal toward the apical aspects until, finally, no foci are visible or, at most, they are limited to the superior portions of the upper lobe. After a number of weeks or months another dissemination is observed and if the patient lives long enough another clearing may occur from below upward. Microscopic studies explain the apparent disappearance of the foci in the roentgenograms. One of the cases in my series had four separate seedings in the course of 15 months. These were demonstrated by x-ray and confirmed by microscopic examination which clearly demonstrated miliary lesions of four separate age groups. If this patient had been admitted to the hospital after the third dissemination had cleared roentgenologically, one would have had the mistaken impression that death had occurred after one seeding and that the foci were all of a recent date.

Not all individuals show clearing of the foci; some show progressively increasing numbers of miliary foci in subsequent roentgenograms—evidence of further disseminations. It has been my experience from serial roentgenographic studies, and from gross and microscopic examinations, that with the exception of those patients who die shortly after their first disseminations, the hematogenous seedings are usually multiple.

Gross Appearance, Distribution and Size. The dissemination in the

lungs is present from the apices to the bases. The foci are larger and more numerous in the apical parts and become smaller and less numerous toward the caudal aspect. They are larger and more numerous in the anterior than in posterior aspects of the individual lobes. Although most of the foci throughout the lung are approximately 1 mm. in size, those in the apico-ventral aspect of the upper lobe may measure 2 to 3 mm. and often have the appearance of acinous foci. Those in the posterior and basal portions of the lower lobes are almost invariably less than 1 mm. in size.

This variation in size and distribution has been variously interpreted by a number of authors. Buhl² and Ribbert³⁵ believed that miliary tuberculosis begins in the apices and progresses toward the bases so that the larger tubercles are the older ones and the smaller are the younger. Roentgenographic studies reveal the fallacy of this view. When dissemination occurs it is diffuse throughout the lung parenchyma. Schmorl²¹ attributed the difference in size to factors which are more favorable for the rapid growth of tubercles in the upper parts of the upper lobe.

The answer to this question may lie in the posture of the lungs. Medlar and Sasano⁴⁵ injected tubercle bacilli intravenously into rabbits and strapped one group in an upright position for 10 hours daily and kept the other group in the normal position. They found that in the latter animals the tuberculous process developed chiefly in the posterior parts of the lung while those in the upright position had a preponderance of the lesions in the anterior areas. In both positions the lesions developed chiefly in the apical portions.

In a recent study⁴⁶ I pointed out the effect of mechanical compression of the lungs (thoracoplasty, artificial pneumothorax, empyema) on the dissemination of foci within the parenchyma. When dissemination occurred in these cases the noncompressed lungs contained the typical miliary seedings; the compressed lung showed none, or a markedly decreased number. Similar is the distribution of foci within lung parenchyma when chronic pulmonary tuberculosis precedes the seedings. The extent of this dissemination depends upon the amount of uninvolved lung parenchyma present before the hematogenous seeding occurs. The miliary foci appear in the previously clear lung tissue and the extent varies from the presence of seedings in all lobes to a distribution of foci limited to the lower part of one or both lower lobes. Foci in the upper lobes are larger than those in the lower lobes.

The most recent dissemination in my series was observed 5 days before death and the oldest dissemination occurred 15 months prior to autopsy examination. Thus the opportunity has been afforded to study

generalized miliary tuberculosis in all stages of development. Only for a limited period after the first dissemination do all the foci appear to be of the same age. In a short time they are of varying anatomic ages because of repeated seedings.

The foci in the earlier stages of development are yellow in appearance and fuse irregularly with a surrounding lung parenchyma which is firm and red. Although some of the tubercles are round or oval, most of them are irregular. In the later stages of development the tubercles are spherical, gray and well demarcated from a surrounding lung parenchyma which is resilient and often emphysematous. These foci represent the older seedings and are smaller than those in the earlier stages. Also usually present throughout the lung parenchyma are yellow foci (more recent disseminations).

Some of the cases in my series afforded the opportunity of studying far-advanced healing. The foci were either invisible to the naked eye or appeared as small gray or gray-black strands of tissue surrounded by emphysematous lung tissue. They were present chiefly in the apical portions of the upper lobes.

Microscopic Appearance. There has been much discussion as to whether the tubercles develop within the alveolar spaces (intra-alveolar) or in the interstitial tissue (interalveolar). My own findings substantiate the former contention. The first change is that of an alveolar filling process composed of polymorphonuclear leukocytes, alveolar phagocytes, occasional red blood cells and variable amounts of fibrin. In many instances fibrin is entirely absent. The alveoli thus involved are from two to five in number. A few of the surrounding alveoli contain alveolar phagocytes, lymphocytes and occasional red blood cells. The capillaries in the interstitial tissue here are dilated and filled with blood; this is the perifocal reaction.

As the process continues the area of pneumonia may either (1) undergo caseation or (2) be invaded by productive elements. (1) In the first instance the exudate within the alveoli and the fixed tissue elements undergo caseation and with the hematoxylin and eosin stain the focus has a pink-blue granular, and later a pink, appearance. The elastica and van Gieson's stain reveals that the elastic fibers of the alveolar septa, blood vessels and bronchioles within the zone of caseation are still intact. Surrounding the area of caseation is a zone of fibroblasts, epithelioid cells, giant cells and collagen fibrils. I have noted that exudate containing fibrin has a greater tendency to undergo caseation. (2) In this case fibroblasts, epithelioid cells, giant cells and collagen fibrils invade the focus. In the earlier stages the alveolar structure is well retained and the productive elements are intermingled

with the exudative components in the alveolar spaces and are present within the walls of the alveolar septa. As the process continues these productive elements within the alveoli replace the exudate and destroy the septal walls. The end result is an oval or round tubercle in which the underlying lung architecture is completely destroyed.

Healing is observed within the miliary tubercles in both types of foci. The peripherally placed productive elements of a focus with a central zone of caseation extend into this caseous center and gradually replace it. As the process continues, the collagen fibrils formed by the epithelioid cells and fibroblasts increase in number and fuse. With this progression a concomitant decrease in the cellular elements results until finally only a concentric zone of hyalinized connective tissue remains. A focus of the cellular type, in its progression to healing, shows an increase and fusion of the collagen fibers with again a disappearance of the cellular elements with the final formation of a concentric zone of hyalinized connective tissue. Subsequently these areas of connective tissue lose their concentric arrangement, become flattened and, with the disappearance of the specific elements, the resultant scars cannot be differentiated from those caused by other inflammatory processes.

As these cellular foci are transformed into hyaline connective tissue they gradually decrease in size. The surrounding alveolar septa which are intimately adherent to them become stretched and, as the tubercles become smaller, tear. This results in alveolar dilatation and even bleb formation around the healing and healed tubercles. The hyperventilation of the areas encircling these healing tubercles and the diminution in the size of the foci themselves cause a partial or complete disappearance of the characteristic x-ray picture of miliary seeding. Since the foci in the basal areas are smaller and less numerous, the fading of the foci from the roentgenogram is noted first in this portion. As healing progresses there is a progressive "resolution" toward the apical region, and if the source of the hematogenous dissemination has been shut off, all the foci disappear permanently from the roentgenogram. The foci, on gross examination, are visible to the naked eye for a long time after they have disappeared from the x-ray field. Very often, however, a new dissemination appears before the previous seeding has completely "resolved" roentgenographically.

Spleen

Gross. With the exception of those cases in which the dissemination is extensive, miliary tubercles are not distinguishable from splenic corpuscles. When perceptible, they appear as gray elevated nodules which stand out above the cut surface as fine granules. They are approxi-

mately 1 mm. in size and in some regions there are larger foci which have a yellow appearance. I cannot agree with Huebschmann¹⁰ that only the inexperienced cannot distinguish tubercles from the splenic corpuscles, the follicles being gray and the tubercles white.

Microscopic Examination. Although sometimes seen in the splenic corpuscles, tuberculous foci are usually present in the splenic pulp. This is in contrast to the findings of Gråberg,⁴⁷ Heitzmann⁴⁸ and Lubarsch⁴⁹ who found tubercles predominantly in the follicles. My observations as to the development of the tubercle agree with those of Huebschmann and Arnold,⁴⁴ Baumgarten,⁵⁰ and Schleussing.⁵¹ The earliest changes observed were those of tissue damage. (Tubercle bacilli are numerous and easily demonstrated in the paraffin section at this stage.) This tissue damage is characterized by focal areas of necrosis in which numerous nuclear remnants give the area a blue, granular appearance with the hematoxylin and eosin stain. The underlying splenic architecture is still discernible within the focus in this stage of development. Polymorphonuclear leukocytes are always present and sometimes, in addition, there are occasional epithelioid cells. The question arises as to whether the stage of primary tissue damage is followed by an exudative phase characterized by the presence of polymorphonuclear leukocytes and fibrin and followed in turn by the productive reaction, or whether it is followed directly by the productive reaction. The difficulty in answering this question lies in the fact that most of the foci when first seen are too far advanced to make discriminating observations.

I tend to agree with Huebschmann¹⁰ who felt that the exudative reaction (polymorphonuclear leukocytes and sometimes fibrin) may either go on to caseation or be followed directly by the invasion of the productive elements. If caseation should develop it is encircled by a narrow zone of epithelioid cells, fibroblasts with occasional collagen fibrils and giant cells. Within the caseated area in the earlier stages nuclear remnants and occasional polymorphonuclear leukocytes are present, an indication that the stage of caseation follows the exudative phase. More frequently have I observed the direct invasion and replacement of the exudative elements by the productive components. The result is the formation of an epithelioid-giant cell tubercle which is oval or round. With the invasion of the productive elements the underlying architecture is rendered indiscernible. Thus the spleen in the fully developed stage is studded with oval and round epithelioid-giant cell tubercles, some of the foci containing central regions of caseation. I have not been convinced that caseation ever follows the productive stage.

Healing of the tubercles occurs under the same circumstances and in the same manner as in the lungs. With the complete hyalinization of the foci all signs of specificity disappear and the origin of the connective tissue cannot be determined.

Kidney

In a generalized miliary dissemination one would expect to find miliary tubercles in 100 per cent of the cases. I believe that the reason why 34.1 per cent of cases are negative lies in the technical difficulty in thoroughly examining the kidneys for tubercles. The negative cases include those in which healing of miliary foci was found in other organs and those in which miliary dissemination was not extensive in the spleen or lungs. I think that my search was sufficiently complete to determine definitely the absence of foci. A thorough search would necessitate sectioning the kidney into 2 or 3 mm. slices, followed by serial microscopic study if no foci were found by such detailed gross examination.

Gross. In cases of diffuse generalized dissemination numerous foci are visible on the surface of the kidney when the capsule is removed. These foci appear as flat yellow areas, usually from 1 to 2 mm. in size, which fuse irregularly with the surrounding renal parenchyma. In the earlier stages a narrow red zone surrounds the miliary tubercles. Upon the cut surface the foci are frequently seen as linear areas which lie parallel to the radial rays. They are most frequent in the cortico-medullary region, less common in the cortex and least numerous in the medulla.

Microscopic Appearance. The development and ultimate fate of the tubercle is similar to that in the spleen.

Adrenal Gland

Although the adrenal glands showed tuberculous involvement in 98 cases, 84 (28.2 per cent) actually contained miliary tubercles. The other cases presented large caseous foci which often caused marked enlargement of the gland. The anatomic picture of these latter foci clearly indicated that their development preceded the miliary dissemination into the other organs. In a number of cases such nodular caseous tuberculosis was limited to one side, and the miliary involvement of the opposite adrenal was similar to that seen in the spleen and kidneys.

Gross. Miliary tubercles are rarely visible in the adrenal gland on gross examination. When they can be seen, they appear as relatively few gray or gray-yellow foci present mainly in the cortex.

Microscopic Appearance. The appearance of miliary tubercles of the adrenal is similar to those of the spleen and kidney. They are most frequently found in the zona fascicularis of the cortex and are usually not numerous.

CONCLUSIONS

As a result of a pathologic analysis of 297 cases of acute generalized miliary tuberculosis, a revised concept of the pathogenesis of the condition is presented for consideration. The invariable presence of caseous lymph nodes in these cases and the analogous situation to that in other infectious diseases lead to the conclusion that the lymphovenous circulation provides the mechanism for miliary dissemination.

The correlation of several roentgenographs with the anatomic appearance of the miliary foci in each patient demonstrated that a hematogenous dissemination of tubercle bacilli sufficient to produce generalized miliary foci is not necessarily an incurable condition. Such correlation demonstrates the almost invariable occurrence of multiple seedings, some or all of which may resolve.

The usual concept, that the concomitant presence of chronic pulmonary tuberculosis and acute generalized miliary tuberculosis is very rare, is not confirmed by this study. This combination occurred in 64.3 per cent of the cases in the series upon which this paper is based.

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CONGENITAL ABSENCE OF THE PERICARDIUM

REPORT OF A CASE *

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Absence, or deficiency of the pericardium is one of the rarer of the congenital malformations. Historically, it is of interest to note that the first case of absence of the pericardium was described by Realdus Columbus in 1559, though this condition was first accurately described by Baillie in 1788. Since then, reports of individual cases have been made occasionally in the literature. The present case brings the total number reported to 74.

This condition, aside from its rarity, possesses through the cases reported a special interest in attempting to throw some light on the function of the pericardium, a subject still presenting a diversity of opinions. The function usually assigned to the pericardium because of its position and relations has been a restraining influence against cardiac overdistention, a view not well supported by animal experimentation or by observation of human cases in which there was a congenital deficiency. But its presence in all mammalian hearts would certainly imply some functional rôle. Eyster, in 1931, suggested that it has a restraining influence against that degree of distention which in long-continued activity would lead to hypertrophy and subsequent degeneration. Beck, in 1931, in an analysis of the reported cases of deficient pericardium, concluded from these studies that there is no evidence to indicate that the pericardium exerts a beneficial effect on the acutely dilating heart and may even at times constitute a grave danger to the mechanics of the circulation, particularly in those cases in which cardio-pericardial adhesions develop.

Watt (1931), in presenting a case of a rare congenital deficiency of the pericardium and in a review of an extensive bibliography, concluded that this condition is not incompatible with a long, active life, free from any special weakness of the heart, and that a separate pericardium is not absolutely essential to the normal functioning of the heart. A secondary function of the pericardium is to provide a nearly frictionless serous sac to facilitate the movement of the heart. This function can be accomplished quite well with the heart in the pleural cavity.

From the developmental viewpoint, a defect in the pericardium may be due to a premature atrophy of the left duct of Cuvier, resulting

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from some anomaly of the circulation of the great venous trunks. This anomaly leads to an arrested development of the pulmonary ridge, resulting in a localized defect of the pleuropericardial septum. This defect would occur in the fifth week of fetal life when the pericardial column begins to separate from the pleural column.

REPORT OF CASE

The patient was a young, adult, white male soldier, 27 years of age, who was 71½ inches tall and weighed approximately 170 lbs. His bony frame was moderately heavy and muscular development good. He was admitted to the hospital with a perforating gunshot wound. The point of entrance was in the nipple line at the level of the fifth intercostal space on the left side of the chest anteriorly. The bullet traversed diaphragm, spleen, and left lower lobe of the lung. Operation consisted of excision and closure of chest wounds and laparotomy. As both respiratory and circulatory collapse were imminent, the failing heart was reached for through a lower perforation in the diaphragm and gently clasped in the hand for the purpose of manual stimulation. At this time it was noted that the heart was free of any pericardial covering and contained in the same serous cavity as the left lung, a condition signifying the absence of a pericardium, which was thus recognized during life.

Autopsy Findings

Necropsy confirmed the observations made at the time of the operation, with the following pertinent findings:

The mediastinum was seen to be in approximately normal position. The anterior surface of the parietal pericardium was absent. Further exposure disclosed a portion of the membrane over the ascending aorta anteriorly, through a distance 3.0 cm. vertically downward from a normal point of attachment at the beginning of the transverse portion of the arch. This portion of the pericardial membrane showed a rounded, smooth, grayish pink edge and continued from a point 3.0 cm. above the base of the aorta downward and to the right, joining the mediastinal tissue and pleural surface at approximately the level of the base of the aorta. Several small, grayish tissue bands were seen between the mediastinal wall and the base of the heart.

Close examination of the medial portion of the afore-mentioned pericardial membrane showed a continuous edge, visible through a few thin connective tissue bands, extending downward parallel and in contact with the surrounding fatty tissue. The membranous edge circled beneath the inferior portion of the base of the heart and continued as a free edge of a second portion of the pericardium at the left inferior side of the base of the heart. This second portion of pericardium measured 5.0 cm. along the free edge which extended from the lower edge of the cardiac base to a point 3.0 cm. below the left auricular appendage. Between this point and the lower edge of the auricular appendage, the membrane appeared to fuse with the visceral pericardium along the

atrioventricular groove. The free edge was slightly concave. The membrane measured 5.0 cm. at the broadest portion, forming a pouch with smooth inner surface. The external surface, between the free edge and the left pulmonary ligament, showed small lobular masses of fatty tissue.

The upper left side of the heart near the base showed a thin, fenestrated membrane extending from the left inferior auricular surface to the corresponding portion of the medial surface of the upper left lobe.

The medial and inferior anterior borders of the heart were covered by a fatty membrane extending from the interior pleural-mediastinal and pleural-diaphragmatic edge, forming a bed of fatty tissue conforming to the shape of the heart. The membrane extending from the anterior mediastinal edge measured 0.5 to 1.0 cm. in thickness and 2.0 to 4.0 cm. in width, and the one from the anterior diaphragmatic edge measured 1.0 to 3.0 cm. The surface of the fatty tissue was lobular, soft, yellow and slightly translucent, without evidence of a fibrous membrane.

The heart weighed approximately 350 gm. The epicardium over the entire anterior surface was faintly grayish and opaque. A more definite area of gray opacity, seen at the anterior surface near the apex and corresponding to the most anterior portion of the wall, measured 4.0 by 2.0 cm. Scattered subepicardial hemorrhages were seen over the posterior surface, the largest 1.0 cm. in diameter. The great vessels and mediastinal structures appeared to be in normal relation. The thymic area was occupied by fatty tissue.

SUMMARY

1. A case of congenital absence of the pericardium is described which was recognized during life and confirmed by autopsy.
2. The condition is compatible with an active, strenuous life.
3. A separate pericardium is not essential to the normal functioning of the heart. The function of a frictionless serous sac to facilitate the movement of the heart can be taken over by the pleural cavity.

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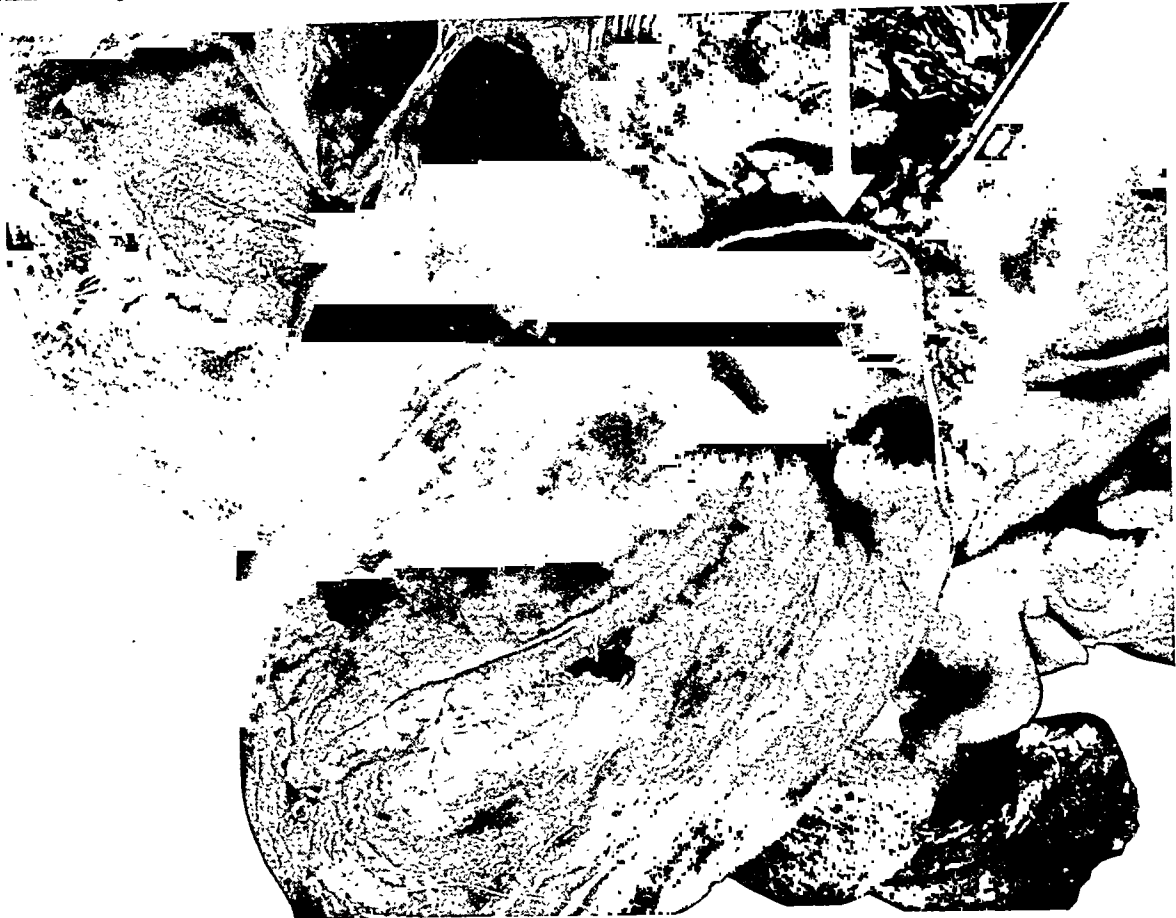
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DESCRIPTION OF PLATE

PLATE 26

- FIG. 1. The heart is shown with retraction of the medial fatty membrane to the right exposing the edge of the pericardial remnant. (Photograph by Signal Corps, U. S. Army.)
- FIG. 2. Left anterior view of the base of the heart with the apex of the heart retracted to the right. Arrow points to the edge of the pericardial remnant which continues to the right under the base of the heart. (Photograph by Signal Corps, U. S. Army.)





CARCINOID TUMOR OF THE CECUM WITH METASTASIS *

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Carcinoid tumor of the appendix is a familiar entity to pathologists and to many surgeons, but the occurrence of carcinoids elsewhere in the gastrointestinal tract appears, from a review of the pertinent literature, to be relatively uncommon. The reported cases of carcinoid tumors of the cecum, particularly, are rare. Stout,¹ in a recent article, reported the distribution of carcinoid tumors of the large bowel and found only 4 occurring in the cecum, all of which he designated as malignant. Mayo and Wilson,² reporting a metastasizing carcinoid of the cecum, found only 3 other carcinoids of the large bowel, all of which had metastasized. Wyatt³ reported 3 carcinoids, 2 from the appendix and 1 from the cecum. The latter had metastasized to the liver.

From an examination of the literature there are found summaries of the reported cases of carcinoids compiled by Forbus,⁴ Cooke,⁵ Ariel,⁶ and Dangremond.⁷ The total number of reported cases is 283, distributed throughout the gastrointestinal tract from the stomach to the rectum. The most common site is in the vermiform appendix, and approximately 85 per cent of all carcinoids occur in the ileocecal region including the appendix and the ileum. Occurrence in the remainder of the small bowel is less frequent. Stout¹ reported 10 cases which were found in the colon and 12 which occurred in the rectum; the latter group includes 6 rectal tumors in that author's series, 5 of which differed cytologically from the ordinary carcinoid. Isolated cases have been described as occurring in the stomach and in a Meckel's diverticulum.

Raiford⁸ reported the incidence of carcinoids in the Pathology Laboratory of the Johns Hopkins Hospital. He found 29 cases among 62,000 specimens, including autopsy and surgical material.

We wish to add the following case of carcinoid of the cecum to the 4 so far reported. In common with these, our case has local and distant metastases.

REPORT OF CASE

The patient, an elderly white male, 72 years of age, had been seen in the out-patient clinic for several years because of vague complaints referable to the gastrointestinal tract. He had been studied thoroughly, including gastrointestinal x-rays and extensive laboratory procedures, but a positive diagnosis was not obtained. He was admitted to the hospital 4 months before death, at which time he again complained of gastrointestinal disorders. The principal physical finding at this time

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was tenderness and rigidity in the right upper quadrant and the abdomen, with a mass which was thought to be an enlarged liver. It was felt that the patient probably had a carcinoma of the gastrointestinal tract which had escaped diagnosis, and a peritoneoscopy was done. Multiple nodules in the liver were noted, the largest estimated to be 4 by 6 cm. These were yellow-white in color and appeared to be neoplastic, but there was no evidence of carcinoma elsewhere. Therefore the diagnosis was made of metastatic carcinoma of the liver, primary site undetermined. The patient had a progressive downhill course and expired.

Necropsy

Gross Examination. The examination of the thorax was irrelevant. The peritoneum was shining, smooth and glistening. The liver weighed 1480 gm. The color was basically deep purple-brown, but the surface was studded with yellow nodules averaging 5 cm. in diameter. Most of these nodules were spherical and were much firmer than the surrounding liver parenchyma. The surface made by cutting showed these nodules to be uniform in color and consistency throughout, and sections through the liver showed the distribution of these nodules to be general throughout all lobes. The cecum was purple to red and slightly distended. The appendix was retrocecal and curved upward and inward and was partly obscured by an adherent spherical mass 2.4 cm. in diameter which appeared to arise from the serosa on the medial aspect of the cecum 8 cm. above the ileocecal valve. It had no connection with the appendix. The surface of this nodule made by cutting was smooth and was yellow to brown. Connected with this mass was a white cord which was firm and approximately 0.3 cm. in diameter and which extended medially. At the point of junction of this cord with the mesentery were many firm, discrete lymph nodes 0.5 to 1.5 cm. in diameter which were yellow to brown. The mucosa of the entire colon and of the small bowel was entirely normal. The examination of the remainder of the abdominal contents showed nothing of importance.

Microscopic Examination. Sections of the cecal tumor showed closely packed groups of cells, which for the most part were polyhedral and round. The nuclei which were oval were deeply stained, and the outline of the cytoplasm was somewhat indistinct. There were some granules in the cytoplasm. Around the borders of these nests there was a tendency toward a palisade arrangement, and these cells had the same nuclear pattern, but they were somewhat columnar in shape. Some cells were arranged in a circular pattern around a cavity or a vesicle and formed a rosette. In these the nucleus was basally placed and the major portion of the cytoplasm was centrally placed toward the vesicle. The individual nests of cells had a fine connective tissue stroma and were separated from each other by coarse fibrous connective tissue bands. Sections of the lymph nodes showed complete replacement of the lymphoid tissue by cells similar to those described. The tumor cells were in smaller nests, and the fibrous connective tissue was

more abundant and of a coarser variety. The rosette pattern was absent. Sections of the liver showed extensive invasion by the same type of tumor. The clumps or nests of cells resembled those found in the lymph nodes. They were uniformly smaller than those in the primary lesion and were separated by dense and coarse connective tissue bands.

Argentaffine granules were demonstrated in the cells of the cecal tumor and in those of the lymphatic and hepatic metastases after the method of Masson.⁹

DISCUSSION

A review of the origin and development of these tumors readily accounts for their sites of predilection. Masson⁹ stated that the structural features of carcinoids are sufficiently uniform, regardless of their location in the alimentary tract, to be grouped under the same title. "From their structure carcinoids were at first thought to be carcinomata; Their usual benignity and their small size earned for them the name little carcinomata (Lubarsch), then carcinoid (Oberndorfer)" Recent reports of metastasizing carcinoids make pertinent the question as to whether they should again be considered as carcinomata.

Carcinoids are composed of epithelial cells which are grouped in nests and in columns. Three different types of cells are found: (1) round or polyhedral, (2) palisade cells which are columnar, and (3) prismatic cells which form rosettes around a cavity or a vesicle. All of these cell types may appear in a single nest together with intermediary forms.

According to Masson,⁹ the final histologic diagnosis of a carcinoid depends on the identification of argentaffine granules in the protoplasm. Stout¹ has described carcinoid tumors in the rectum composed of the pre-enterochrome cells of Erspamer. These differ cytologically from carcinoids of the usual type.

The recognition of carcinoids is often incidental at autopsy. Many of these tumors are small and produce no symptoms. Others occurring in the small intestine produce symptoms of intestinal obstruction which are usually the result of a kinking or intussusception rather than of actual constriction such as is seen in carcinoma. Other clinical findings may be diarrhea, anorexia, loss of weight, abdominal pain and weakness. Melena is rarely encountered since these tumors rarely ulcerate.

It is generally considered that carcinoids are benign neoplasms since many which occur in the appendix remain entirely localized. However, a considerable number have been described with metastases to the mesentery, regional lymph nodes, lungs, liver, spleen, adrenals, kidney, brain and bone marrow. Cooke⁵ emphasized the potential malignant character of carcinoids and included 21 metastasizing tumors of this nature in his series.

Mayo and Wilson² recently reported their case as adenocarcinoma grade II of the "carcinoid" type with involvement of the regional lymph nodes, and Wyatt³ stated that all carcinoids must be considered to be slowly growing malignant tumors. From the consideration of the case herein reported, it appears that the benign nature of carcinoids has been somewhat overemphasized.

We find some difficulty in explaining the occurrence of the tumor in our case outside the serosa of the cecum, although the tumor reported by Mayo and Wilson² appears to have been similarly situated.

SUMMARY

A fifth case is added to the reported series of carcinoid tumors of the cecum.

In common with those previously reported, our case had local and distant metastases.

It is suggested that the term "carcinoma of the carcinoid type" be substituted for the term "carcinoid."

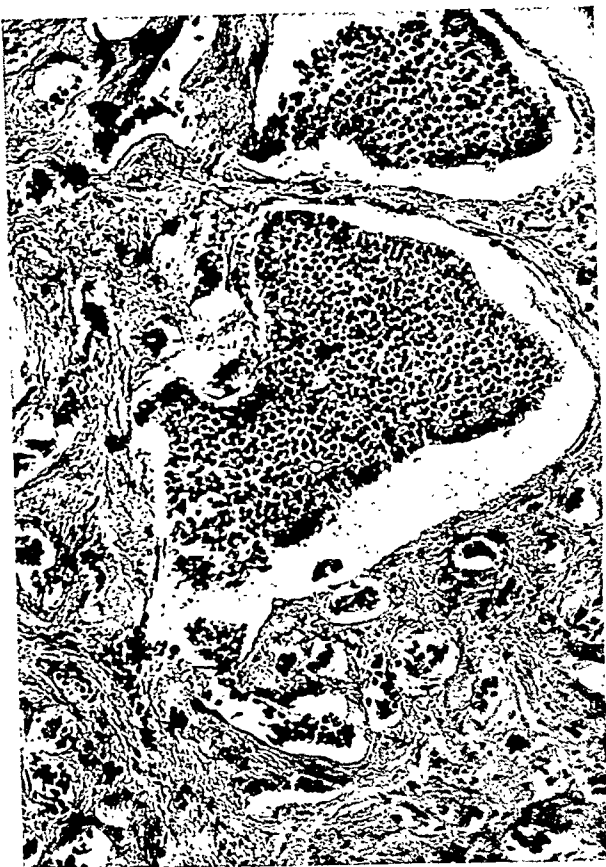
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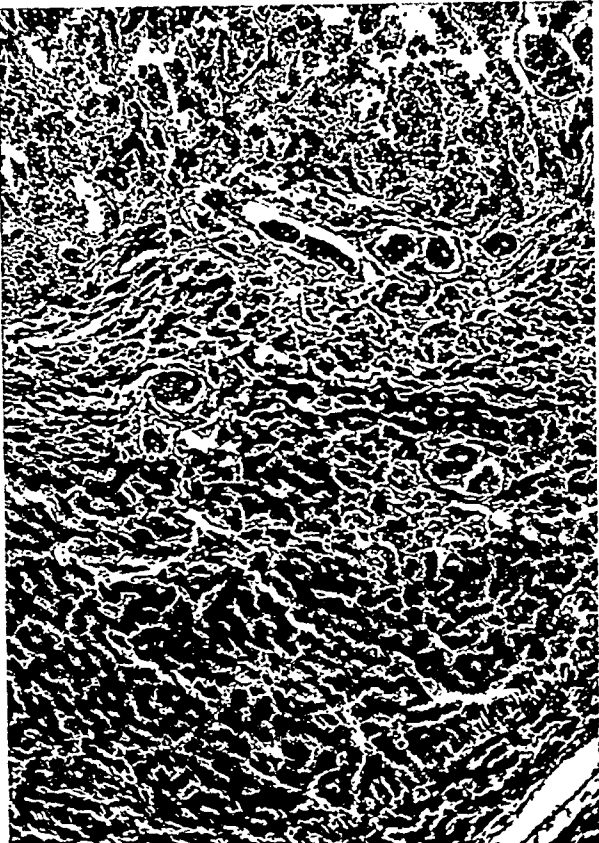
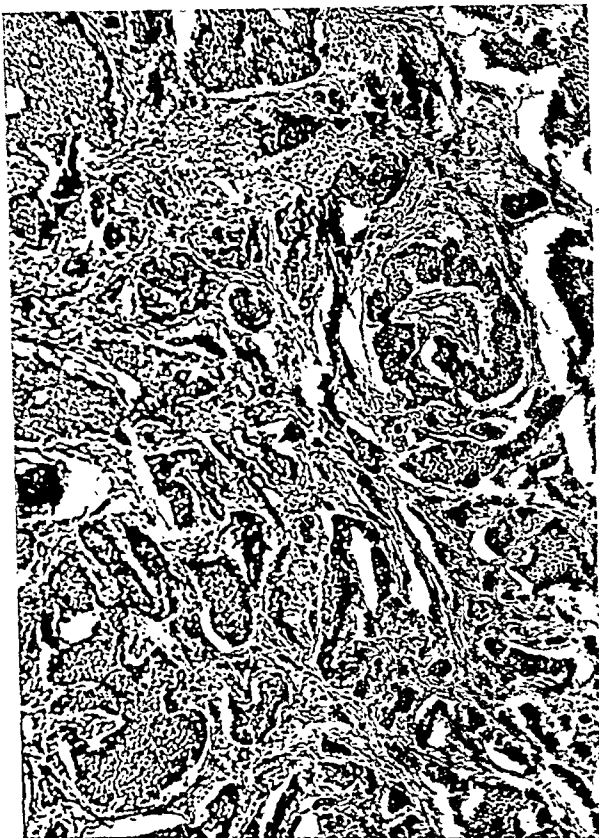
DESCRIPTION OF PLATE

PLATE 27

- FIG. 1. Section through the cecal tumor. All three cell types are found in the larger nests: round and polyhedral, columnar, and rosette types. The fibrous partitions are coarse. Masson's trichrome stain. $\times 129$.
- FIG. 2. Higher magnification of a field in Figure 1 showing the palisade arrangement and the rosette formation. Masson's trichrome stain. $\times 515$.
- FIG. 3. Section through a lymph node showing complete replacement of the lymphoid tissue by nests of carcinoid cells and connective tissue stroma. Masson's trichrome stain. $\times 64$.
- FIG. 4. Section through the liver showing invasion by many small nests of carcinoid cells. Masson's trichrome stain. $\times 64$.



2



4

Potter and Docter

Carcinoid of the Cecum

CEROID, THE PIGMENT OF DIETARY CIRRHOSIS OF RATS ITS CHARACTERISTICS AND ITS DIFFERENTIATION FROM HEMOFUSCIN *

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A peculiar pigment occurring in rats fed choline-deficient diets has been reported from several laboratories. Lillie, Daft, and Sebrell¹ described a coarsely globular pigment which occurred in phagocytes in the cirrhotic livers of rats fed low protein (4 per cent), low fat (5 per cent) diets. In subsequent papers²⁻⁴ they reported its occurrence in liver cells, lung, spleen, lymph nodes, bone marrow and adrenal cortex. They were able to prevent its production by supplementing the basal diet with choline, methionine, and casein singly or in combination. They named the pigment "ceroid"⁴ because of its wax-like appearance and behavior. Blumberg and McCollum⁵ and Blumberg and Grady⁶ reported a similar pigment in the cirrhotic livers of rats fed low protein, high fat diets. Edwards and White⁷ reported a similar pigment in the livers of rats fed low protein diets supplemented with the carcinogen, p-dimethylamino-azobenzene (butter yellow). In a subsequent paper, White and Edwards⁸ reported the pigment in rats fed the basal diet without butter yellow. Smith, Lillie and Stohlman⁹ produced cirrhosis but no ceroid in rats fed high protein diets and butter yellow. György and Goldblatt¹⁰ found a similar pigment in the cirrhotic livers of rats fed low protein, high fat diets.

In view of the specific occurrence, peculiar properties and possible metabolic significance of this pigment (henceforth referred to as ceroid), it seems proper to characterize it more fully. The following observations were made in this laboratory upon liver fixed in formaldehyde and embedded in paraffin.

(1) As previously reported,⁴ ceroid occurs as globules varying in diameter from 1 to 20 μ . These are seen occasionally in liver cells but ordinarily in large rounded phagocytes. The phagocytes usually contain several globules and are seen in greatest number in the liver. In minimal cases a few phagocytes are seen between liver cell cords or surrounding central veins, or rarely in portal areas. In moderate to marked cases, numerous phagocytes form broad sheets and trabeculae which divide and encircle nodules of liver cells. Ceroid has been seen in phagocytes in alveolar septa of the lung, in splenic pulp, bone marrow, lymph nodes and adrenal cortex. A substance with similar staining re-

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actions occurs as rims or halos about large fat vacuoles in the liver. The large vacuoles are presumed to lie in liver cells.

(2) In sections stained in hematoxylin and eosin, van Gieson's connective tissue stain, Masson's trichrome stain, and in sections immersed for 1 hour in 1/1000 aqueous acid dyes: naphthol green B, orange G, congo red, trypan blue, tartrazine [C.I. no. 640], acid fuchsin, eosin Y, eosin B, erythrosin bluish, phloxine B, rose bengal, nigrosin W.S., alizarin rubinol [C.I. no. 1091], alizarin saphirol [C.I. no. 1054], indigo carmine, and orcein, and in paraffin or celloidin sections mounted unstained, the ceroid appears as pale yellow globules.

(3) Eosin and polychrome methylene blue stain ceroid yellowish green to greenish blue. It is stained slowly by a number of basic dyes when immersed for 1 hour in 1/1000 aqueous solutions. The following dyes all stained ceroid: Bismarck brown, malachite green, brilliant green, pararosanilin, basic fuchsin, new fuchsin, methyl violet, crystal violet, methyl green, safranin O and D, methylene violet RRA, brilliant cresyl blue, Nile blue A, methylene blue, toluidine blue, and cresyl violet. The slowness with which ceroid is stained by basic aniline dyes may explain Edward and White's⁷ failure to stain it in fuchsin and in phloxine methylene blue.

(4) It is strongly acid-fast. When stained with steaming Ziehl's carbolfuchsin for 10 minutes, the bright red globules resist decolorization in 3 per cent hydrochloric acid in 70 per cent alcohol for at least 2 days.

(5) It gives several reactions for fat. It stains brownish orange to orange-red with sudan IV in frozen sections. With sudan brown, it stains brownish orange. In paraffin sections the sudanophilia is retained provided the sections are mounted in the usual fat-stain mounting media. In the Lorrain Smith Nile blue sulfate stain for differentiating neutral fats, many ceroid globules stain reddish purple while a few are blue, but if such sections are mounted in xylol clarite, most of the globules turn blue in a day or two (paraffin sections). In frozen sections, some are blue while most are reddish purple. Ceroid is black after treatment of paraffin sections or formaldehyde-fixed blocks with osmic acid, with or without antecedent chromation.

(6) It is stained red in Mallory's stain for hemofuscin. In this connection it was noted that 1/1000 aqueous basic fuchsin failed to stain ceroid in 5 minutes, stained a few globules in 10 minutes and stained almost all globules in 30 minutes.

(7) It is negative for iron with both the acid ferrocyanide test of Perls and the ammonium sulfide-Turnbull blue method.¹¹

(8) Ceroid is gram-negative in Weigert's stain for fibrin and bac-

teria, in Lillie's ¹² acetone technic, and in Lillie's ¹³ thiosulfate technic. When stained for 2 hours in hot crystal violet and then treated with iodine and acetone, ceroid stains violet rather than the blue-black of gram-positive bacteria.

(9) It stains gray to black in Weil's modification of Weigert's stain for myelin.

(10) It reduces silver nitrate very slowly and irregularly. Foot's ¹⁴ diamino-silver carbonate solution is reduced in 48 to 96 hours, giving brown to black ceroid globules.

(11) In paraffin sections, ceroid does not reduce ferric chloride-ferricyanide in Schmorl's ¹⁵ test for "Abnutzungspigmente."

(12) It is stained a light brown by Gram's iodine.

(13) In ultraviolet light under the fluorescence microscope, the globules of ceroid display a greenish yellow fluorescence which changes slowly to a yellowish white fluorescence. The fluorescence is displayed by frozen sections and by paraffin sections dry, in water, or in paraffin, but not in xylol or xylol clarite.

(14) It is not removed from paraffin sections by prolonged treatment in water, alcohols (methyl, ethyl, propyl, or isopropyl), acetone, ether, chloroform, benzene, xylene, gasoline, propylene glycol, hydrogen peroxide, chlorine water, potassium permanganate, dilute acids (hydrochloric, sulfuric, acetic, nitric), or dilute alkalies (sodium hydroxide, sodium carbonate, ammonium hydroxide).

(15) In autolyzed material, where basophilia is poor, this staining quality of ceroid is improved by post-formaldehyde block mordanting with picric acid, or in paraffin sections by treating with potassium permanganate followed by oxalic acid, by treating with picric acid, or by treating with iodine followed by thiosulfate.

(16) When a formaldehyde-fixed liver is ground with mortar and pestle, suspended in distilled water and allowed to stand overnight, the ceroid settles out in a sharply defined layer of bronze-brown viscid material just above the liver debris from which it may be separated in a separatory funnel. When extracted with chloroform, ether and acetone and evaporated to dryness this material yields a coarsely granular, dark brown residue. The residue, when crushed on a slide in a drop of water and examined microscopically, is seen to consist of ceroid globules and a little cellular debris. This crude concentrate reacts to stains and solvents in the same manner as ceroid in paraffin sections. It is decomposed by concentrated mineral acids and strong alkalies. It chars but does not melt on heating. It gives a negative Gmelin reaction and produces no color reaction in the chloroform-sulfuric acid test for carotenoids. It is slowly dissolved in boiling 10 per cent sodium hydroxide

from which a fatty substance is precipitated on neutralization with hydrochloric acid.

DISCUSSION

The chemical nature of ceroid cannot be fully stated at present. Several theories as to its composition have been advanced by other laboratories and will be discussed briefly.

Blumberg and Grady⁶ regarded the pigment as hemofuscin. However, von Recklinghausen,¹⁶ who first described hemofuscin, characterized it as a gall brown, very finely granular, iron negative pigment which occurs in hemochromatosis along with large amounts of hemosiderin. He found it in smooth muscle of the intestines and blood vessels, in mast or connective tissue cells of the vascular supporting tissue (Glisson's capsule, etc.) and in certain cells of the salivary and lacrimal glands. Hemofuscin, as previously described and as further characterized by Mallory, Parker and Nye,¹⁷ has been studied in this laboratory in material from cases of hemochromatosis, some of which was furnished us by the Curator of the Army Medical Museum. It was found to differ from ceroid in appearance, location and staining. It is not acid-fast, stains readily with dilute basic aniline dyes and is not sudanophilic after paraffin embedding.

Edwards and White⁷ suggested that it may be a conjugated lipid. György and Goldblatt¹⁰ advanced the theory that it may represent a lipid conjugated with a protein and may arise from necrotic remnants of liver cells. Available evidence lends some support to these theories. Ceroid gives several reactions for fat. It is not, however, soluble in ordinary fat solvents and, furthermore, demonstrates staining reactions not shared by neutral fat, ordinary fatty acids and the simpler lipoids.

In this laboratory it has been observed in cases of progressive cirrhosis as small globules within apparently surviving and often fat-free liver cells, suggesting that it may be a product of altered liver cell metabolism, but it also occurs as acid-fast, basophile rims about obvious coarse fat globules probably located in distended liver cells, suggesting origin also from what, in earlier stages of the process, appears to be neutral fat. Similar acid-fast material originating from foreign fat has been reported in cod liver oil pneumonia,^{18, 19} but the further agreement of this material with ceroid has not been fully established.

Ceroid has shown no properties which would justify classing it with anthocyanins, sterols, carotenoids, porphyrins, or the hemoglobin derivatives.

Material furnished this laboratory by Blumberg and by Goldblatt contains a pigment indistinguishable from the ceroid in our own material.

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FURTHER STUDIES ON THE PREGLOMERULAR CELLULAR APPARATUS *

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When, in 1927, I described the existence of a preglomerular cellular apparatus in the human kidney, I pointed out three main facts: (1) the constant presence of special cells in the afferent arterioles of the normal kidney and their principal morphological characters, especially their fuchsinophilic granulations; (2) their identity with the so-called neuromuscular cells in the vascular glomera as described by Masson; (3) their possible relationship to the mechanism of hypertension. Since then this cellular apparatus has been studied in numerous publications and the various views expressed on this subject as well as some new developments concerning the significance of these cells have been reviewed recently by H. W. Smith in his Harvey Lecture on renal circulation.

Upon reading this study one cannot but be impressed by a series of conflicting statements concerning this cellular apparatus. The existence of cells, which is affirmed by some authors, is denied by others, and often one has the impression that statements referring to certain structures are implicitly applied to others for which they have never been claimed. The main reason for this confusion is that, curious as it may be, most of the authors, including myself, who have first studied these cells were unaware of previous publications concerning the same or similar elements. Different technics were applied which did not always give the same results. Analogies were established which, upon closer examination, proved to be far from obvious and, finally, theories were advanced which from the beginning lacked all material proof. The picture thus created appears rather confusing.

The principal facts may be summarized as follows. Ruyter first called attention to structural peculiarities of the afferent glomerular artery characterized by a disappearance of the internal elastic membrane and by a thickening of the muscular layer due to the presence of granular cells. These cells seem to originate from muscular elements which in successive states of transformation change the shape of their nuclei, lose their fibrils and acquire acidophilic granulations. Ruyter studied these cells in mice; he was able to see them also in rats but he stated explicitly that he could not find them in the kidneys of man, monkey, dog, cat, rabbit, or guinea-pig.

* Received for publication, March 29, 1943.

Two years later, unfamiliar then with Ruyter's paper, I described the cellular apparatus in the afferent artery of the human kidney, made up of elements of which I gave the following characterization: "At first sight they seem almost spherical or polygonal but on closer examination they seem to emit protoplasmic expansions interlaced with those of the neighboring cells. . . . The nucleus, containing a very delicate chromatin network, is spherical or somewhat indented. The cytoplasm is relatively clear and contains fine acidophilic granulations. These granulations exist constantly." Subsequently, these cells were identified by Goormaghtigh with those studied by Ruyter in mice, and Goormaghtigh himself found granular cells in various animals, especially in the rabbit in which Ruyter had been unable to detect them. The homology of all these cells, convincing as it may appear, remains still to be proved because the cytological aspect of the granular cells in the afferent arteriole is not at all the same in various species and it is quite possible, as we shall indeed see later, that different types of cells have to be distinguished. Nevertheless, Goormaghtigh's study seemed to have clarified the question somewhat until new confusion was created by Zimmermann's article on the so-called "Polkissen" cells in the mammalian kidney. The elements described under this denomination are spherical, or slightly elongated, clear cells occupying the place of the muscular cells in the media and often grouped in multiple layers around the endothelium. At the arteriocapsular junction they often form an eccentric thickening of the vascular wall, giving rise to a structure which Zimmermann compares to a cushion. Zimmermann was not familiar with my publication on the granular cells in the human kidney but he repeatedly referred to Ruyter's paper. Concerning the relationship between his "Polkissen" cells and Ruyter's cells, he made no clear-cut statement. He admitted that Ruyter must have seen the "Polkissen" cells when he described the special structure of the afferent arteriole, but he repeatedly insisted upon the fact that the cells described by him are devoid of granulations. This statement, however, appears considerably weakened when one looks at Figure 5 of his article in which granular cells, absolutely identical with those described by me in the human kidney, are clearly depicted.

All seem to agree that the afferent arteriole, especially in the vicinity of the glomerular junction, offers some structural peculiarities due to the presence of cells described as granular by some and as clear by others. Actually, both types of cells may be present and I shall consider them separately.

Granular cells exist without doubt in many species, man, guinea-pig, cat, dog, rabbit, rat, mouse; but it must be admitted that the aspect

of these cells varies to a considerable degree. For the study of this question the technic is of great importance and the best results are obtained with the method I indicated in my first publication: fixation of absolutely fresh material in Zenker's fluid-formaldehyde solution and Masson's trichrome staining with hematoxylin, fuchsin and aniline blue. With this technic Ruyter's cells stand out clearly and appear to be filled with voluminous, brightly stained red granules. The cells in the human kidney are larger and their granulations, distinctly fuchsinophilic, are much more delicate and scattered. Incidentally, one can understand that Ruyter, accustomed as he must have been to the bright aspect of the granular cells in the mouse kidney, failed to find similar elements in human material. It might have been also that the human kidneys at his disposal were imperfectly fixed or stained. I have often noticed that in kidneys fixed some time after death or in formaldehyde solution, the granulations are absent and the cells appear to have a clear vacuolar cytoplasm. There are thus two types of granular cells, the mouse type and the human type, and the cells in the various species resemble either one or the other.

But there is another very important discrimination which has to be made and which concerns the histochemical reactions of these granulations. In the rabbit especially, but also in other species, granular cells may be observed not only in the afferent arteriole but also in other vessels of the kidney, with distinctly metachromatic granules easily stainable with toluidin blue. These cells are evidently different from those described by Ruyter and by myself. They are mastocytes. This fact, as we shall see, is of great importance in the conception of a secretory activity connected with the granular cells. For the moment, it is interesting to note that mastocytes, which according to Masson are a constant finding in digital glomera, occur also in the renal arteries in contact with glomic structures. The presence of these cells in such delicate and important vascular organs might be connected with their ability to secrete heparin and in this way to prevent thrombus formation.

What, then, is the significance of the other granular cells? In this respect it is interesting to note that both Ruyter and myself referred to these elements as characteristic for the so-called glomic structures in arteriovenous anastomoses, but that our references appeared to be rather inconsistent. Ruyter compared his cells with the "epithelioid" cells described by v. Schumacher in the coccygeal glomus. But v. Schumacher in his studies never mentioned granular cells. He always described clear cells and insisted repeatedly upon the absence of granulations. In my description, I referred to illustrations presented by

Masson (1924) in his article on digital glomera and glomus tumors. Figures 2 and 5 in this article show glomic cells with distinct acidophilic granulations, and it was because of these pictures that I affirmed the identity between the granular cells in the kidney and the neuromuscular elements in the glomic organs. I was surprised at that time that Masson apparently did not pay attention to these granulations in his text. Upon a recent personal inquiry, Masson re-examined his preparations and informed me that in his opinion the elements depicted are not granulations at all, but merely transverse sections of myofibrils. The granulations, however, in the human kidney cells and also those in mouse kidneys are certainly true granulations and not sectioned fibers. But Masson admits that "in some glomic tumors (never in normal glomi) I have seen cells filled with purely acidophilic granulations without any affinity for the basic blues. These cells are certainly modified tumor cells and it is not impossible that they are of the same nature as those which you have observed in the human kidney."

The granular cells which were considered by Ruyter and by myself as characteristic elements of glomic structures appear to be nonexistent in normal arteriovenous anastomoses. They are a special feature of the preglomerular apparatus in the kidney but they may occur in glomus tumors. Their real significance is unknown. Like the clear cells they may be transformed muscle cells. Ruyter has observed all transitional states between muscle cells and granular elements and it is known that under certain circumstances, as in some tumors, muscle cells may assume a typical granular aspect. Murray and Stout, in a recent study, based upon the behavior of glomus tumors in tissue cultures, have identified the so-called epithelioid cells with Zimmermann's pericytes. I have never been able, however, to obtain an impregnation of the granular cells in the kidney with Kopsch's method, used by Zimmermann for the demonstration of pericytes, and it appears to me that as far as the preglomerular apparatus is concerned the identification with pericytes is very doubtful.

Besides the granular cells, the afferent arteriole may contain in its preglomerular portion a certain number of clear cells, as pointed out by Zimmermann. The difference between the two cell types is merely the presence or absence of granulations and if we consider the fact that, in the human kidney at least, the granulations are often few in number and located in a limited region of the cytoplasm, it may be very difficult to state whether a cell belongs to one type or another. In the human kidney, most, if not all, cells of the preglomerular apparatus are granular. Very probably the granular cells are closely related to, if not identical with, the clear cells. Both the granular cells and the

clear cells are connected among themselves by cytoplasmic expansions and they are only imperfectly separated by a loose reticular network. In this respect they show exactly the same behavior as the so-called epithelioid cells in the glomic organs.

This fact must be remembered in order to avoid the confusion which has been created between the epithelioid cells in glomic structures and clear muscle cells. Under certain still undetermined circumstances it happens that smooth muscle cells, especially in vascular walls, take a clear aspect. This is seen especially in arterial walls undergoing hypertrophy, as was recently shown in an eclamptic kidney by Graef. But those muscle cells are distinctly separated by fine collagenous membranes and have no relation to the epithelioid cells in arteriovenous anastomoses.

The whole structural modification which characterizes the pre-glomerular portion of the afferent arteriole—the disappearance of the internal elastic membrane and the replacement of the muscular elements by epithelioid cells—closely resembles the distinctive morphological features of a glomic vessel. Such an identification, however, would be incomplete without a special consideration of the nervous connections. The studies of Stoerk, Dogiel and Masson have shown the extreme development of nervous plexus and sensory end-organs in contact with glomic vessels. Masson, especially, has described the connections of the nerves in digital glomera with the arterial, venous and dermal plexuses and called attention to the close relationship between the so-called epithelioid cells and the richly developed nervous plexus surrounding the adventitia of the glomic vessels. In accordance with his opinion, the nervous elements and especially the Schwann cells are in morphological continuity with the epithelioid cells, so that it is often impossible to draw a definite line of demarcation. Also, these close connections seem to confer on the glomic cells some sort of "neurility" or conductivity, perhaps not unlike that existing in the cells of Hiss' bundle with which, incidentally, they have, owing to their intercommunications and their clear appearance, some morphological resemblance.

It appeared to be of fundamental importance to study the nervous connections of the preglomerular apparatus; but from the beginning I met with considerable technical difficulty. Only impregnations can give reliable pictures of the delicate nervous structures involved and these technics, as everybody knows, are particularly hazardous as far as vascular nerves are concerned. In fact they seem even more difficult in the kidney than elsewhere. I have tried Bielschowsky's method and multiple variations without the slightest success. Cajal's chloral

method, which gave remarkable results in Masson's work on digital glomera, was ineffective in the kidney arterioles. Finally I obtained some successful impregnations by the Gros-Schultze technic* but, here too, hundreds of sections had to be prepared to obtain even a small number of satisfactory impregnations.

Frozen sections of human kidneys fixed in a 4 per cent solution of formaldehyde were washed for 30 minutes in two baths of distilled water. Some drops of nicotine (5 drops to 30 ml. of distilled water) were added to the first bath. The impregnation was carried out in 20 per cent silver nitrate for 10 minutes and then sections were passed for 20 minutes through 5 successive baths of 8 per cent formaldehyde. They were then immersed for 1 to 3 minutes in a 20 per cent Fontana solution, run through ammonia water, acetic water and finally toned for 1 hour in 1 per cent gold chloride. I found it preferable always to employ freshly prepared Fontana's solution. Congested kidneys in general gave unsatisfactory results.

With this technic I obtained in several instances good impregnations of the perivascular nerves which show the existence of a highly developed nervous plexus around the preglomerular portion of the afferent arteriole. This plexus seems to be made up mostly of two branches, one accompanying the afferent arteriole from its origin and another coming in laterally from the interstitial spaces of the surrounding parenchyma. Upon meeting, these branches form a dense network of fibers which gives rise to nerve endings in contact with the cells of the arterial wall. Some of these fibers are coarser and may well be myelinated though I was never able to show myelinated nerves up to the preglomerular portion of the afferent arteriole. The plexus is again split up. Some small fibers appear to penetrate into the glomerulus; others are directed towards the peripheral leaf of the capsule; the main portion turns around the glomerulus and quickly divides in the interstitial tissue of the surrounding parenchyma. Owing to the fact that I was unable to demonstrate nerve endings in the epithelial cells by the Gros-Schultze technic, it is impossible to say whether all of these nerves are purely vascular or whether this plexus is connected with so-called secretory nerves.

There can be no doubt that the preglomerular portion of the afferent arteriole is richly innervated and these results complete the histological picture of a glomic vessel. The special cells located in this portion of the vessel build up a neuromuscular sheath, as I pointed out in my first communication. They constitute a peripheral vasomotor organ,

* Mallory, F. B. *Pathological Technique*. W. B. Saunders Co., Philadelphia, 1938, pp. 227-228.

the localization of which, at the entrance of the glomerulus, is of obvious significance. It is known that the renal glomeruli are intermittently functioning organs. The activity of this vasomotor organ regulates the glomerular circulation in diverting more or less blood from the glomerulus to Isaac-Ludwig's artery* or towards communicating branches which, according to Kosugi, exist between the afferent and efferent arterioles. At all events the preglomerular apparatus seems to fulfill the function common to all glomic organs, which is the alternating exclusion of a certain capillary territory under the close control of the nervous system.

We come now to the second point of our discussion which concerns the relationship between the preglomerular apparatus and hypertension.

Since I first studied this structure my attention has been focused on this problem, and in hundreds of cases I have tried to compare the development of the preglomerular apparatus in kidneys of normal and hypertensive patients. I soon realized the difficulties and the unavoidable shortcomings of such a comparative study. The preglomerular apparatus is very irregularly developed in the various afferent arterioles. Moreover, the cells are generally accumulated at one side of the vessel so that for each glomerulus there is only one plane of sectioning which gives the complete picture of the apparatus. In an average kidney section, containing about one hundred glomeruli, there are only five or ten which give a fairly accurate impression of these vascular structures. Even if these one hundred glomeruli are examined in serial sections, this gives only a 1 to 10,000 approximation of the situation in the whole kidney. Obviously this is insufficient to make any precise statement about the development of the preglomerular apparatus and to establish comparative figures.

Furthermore, there are still many imponderable factors involved. The same fixation does not always give the same results. It so happens that sometimes the cells are poorly fixed, the granulations are not visible, the cytoplasm is uniformly clear and vacuolar and often the cell boundaries disappear so that the whole structure becomes indiscernible to even an experienced observer. Comparative studies become more or less a question of personal impression and the results may show surprising variations if, as I have done repeatedly, whole series of cases are submitted to different observers.

The results of these studies carried out in France as well as in this country may be summarized as follows. The preglomerular apparatus shows appreciable variation in its development in various persons but

* Smith, H. W. Physiology of the renal circulation. *Harvey Lectures*, 1940, 35, 166-222.

there is no parallelism whatsoever between the degree of development and hypertension. Considerably developed structures with abundant granular cells may be seen in children and adults without any elevation of the blood pressure.

In cases of hypertension with hyaline degeneration of the afferent arteriole, the preglomerular apparatus is often well preserved. Sometimes one even has the impression of a certain degree of hyperplasia. But when the arteriolar lesions are more pronounced the apparatus is almost always affected. Fat infiltration of the cells is often present. The granulations disappear and the nuclei become pyknotic. Finally the cells disappear. In the malignant forms of hypertension I always found the cells degenerated or completely destroyed.

These findings are in opposition to those of Elaut and Goormaghtigh. Elaut, in 1934, reported hypertrophy of the epithelioid cells in dogs rendered hypertensive by denervation of the aortic arch and the carotid sinus. Goormaghtigh (1939) then carried out research along the same line and confirmed Elaut's findings, but in subsequent studies laid more and more emphasis upon the glandular nature of the granular cells. In dogs and rabbits made hypertensive by the Goldblatt-Grimson technic* he noticed a considerable hyperplasia and multiplication of the granular cells which appear all over the arterial system in the kidney from the hilum to the glomerular tufts. The cells proliferate so abundantly that their accumulation causes mechanical circulatory troubles. Furthermore, they show not only acidophilic but basophilic granulations and fat droplets, suggesting a real secretory cycle as distinct in Goormaghtigh's opinion as the one observed in the glandular cells of the pituitary body. Owing to the fact that the stimulation of these cells appears to be the distinctive feature of hypertension, Goormaghtigh concluded that these granular cells form an endocrine gland scattered through the kidney like the Langerhans' islands in the pancreas and that their main function is the secretion of the hormone-like pressor substance, renin.

The main objection I can make with regard to these conclusions is that in human kidneys I have never observed pictures like those described in dogs and rabbits. Furthermore, if renin is responsible for hypertension it is surely not secreted by the granular cells of the preglomerular apparatus owing to the fact that in the severest cases of hypertension these cells are generally degenerated. But there are other possibilities which might well explain Goormaghtigh's observations. When we read that the granular cells which proliferate in those kidneys

* Grimson, K. S. The onset of renal ischaemia hypertension induced by readily adjustable renal artery clamps. *J. Physiol.*, 1939, 95, 45-P to 46-P.

contain granulations of all kinds and especially basophilic ones; and that they form, by their accumulation, bulging pads in the intima which secondarily are infiltrated by fats, degenerate and form sclerotic plaques, then it becomes almost evident that these cells are mastocytes and histiocytes. The whole process described therefore has nothing to do with the preglomerular apparatus. It is merely one of muscular hypertrophy and of arteriosclerosis of the renal vessels and it becomes difficult to see here the activity of endocrine elements responsible for the increase of the blood pressure. These lesions are probably a result of hypertension and not its cause.

In rejecting Goormaghtigh's interpretations I am far from ruling out the intervention of the preglomerular apparatus in the mechanism of hypertension, but in my opinion the available data point in a direction just opposite to that indicated by Goormaghtigh. The regressive changes which the preglomerular apparatus undergoes constantly in advanced and severe cases of hypertension indicate the suppression of a delicate regulatory mechanism placed at the entrance of the glomerular circulatory system. It is well known that at a certain moment hypertension, which may be, for long years, a reversible phenomenon, becomes stabilized at a high level and it is not impossible that the destruction of the preglomerular apparatus is connected with this change which plays such an important rôle in the evolution of the disease.

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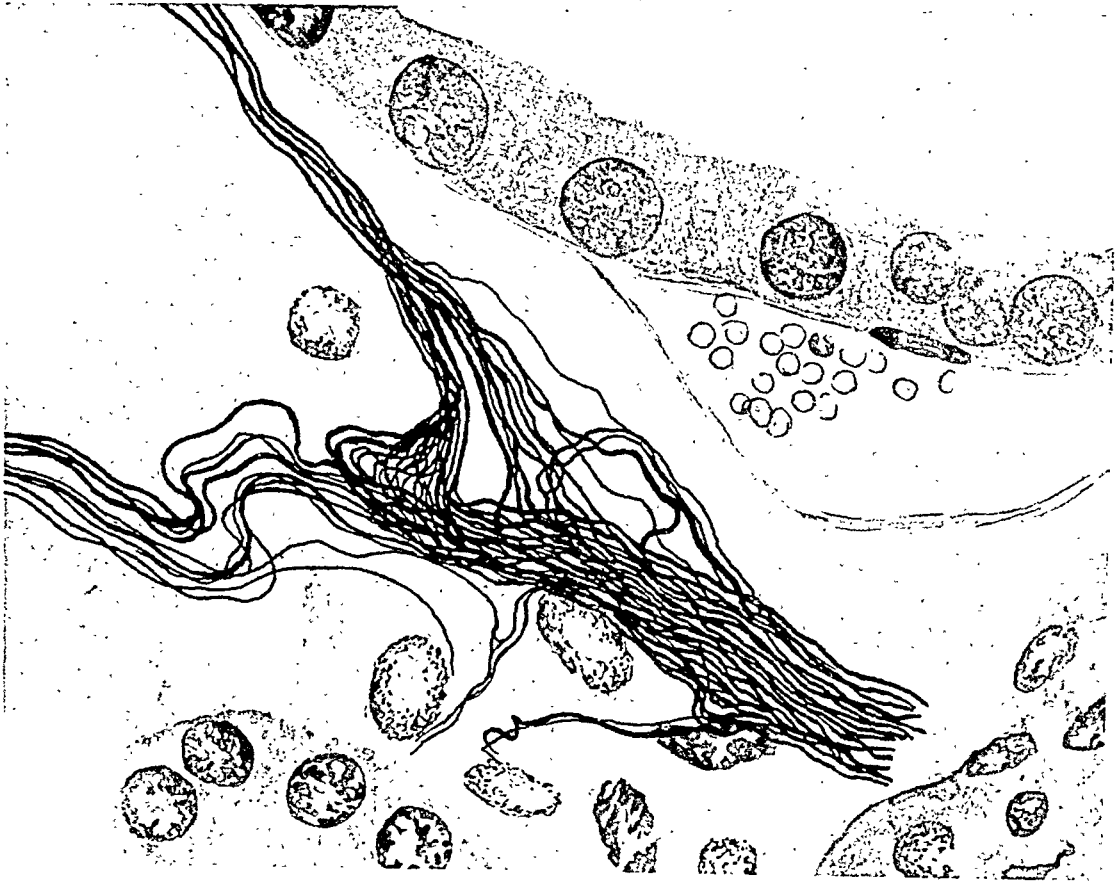
DESCRIPTION OF PLATES

PLATE 28

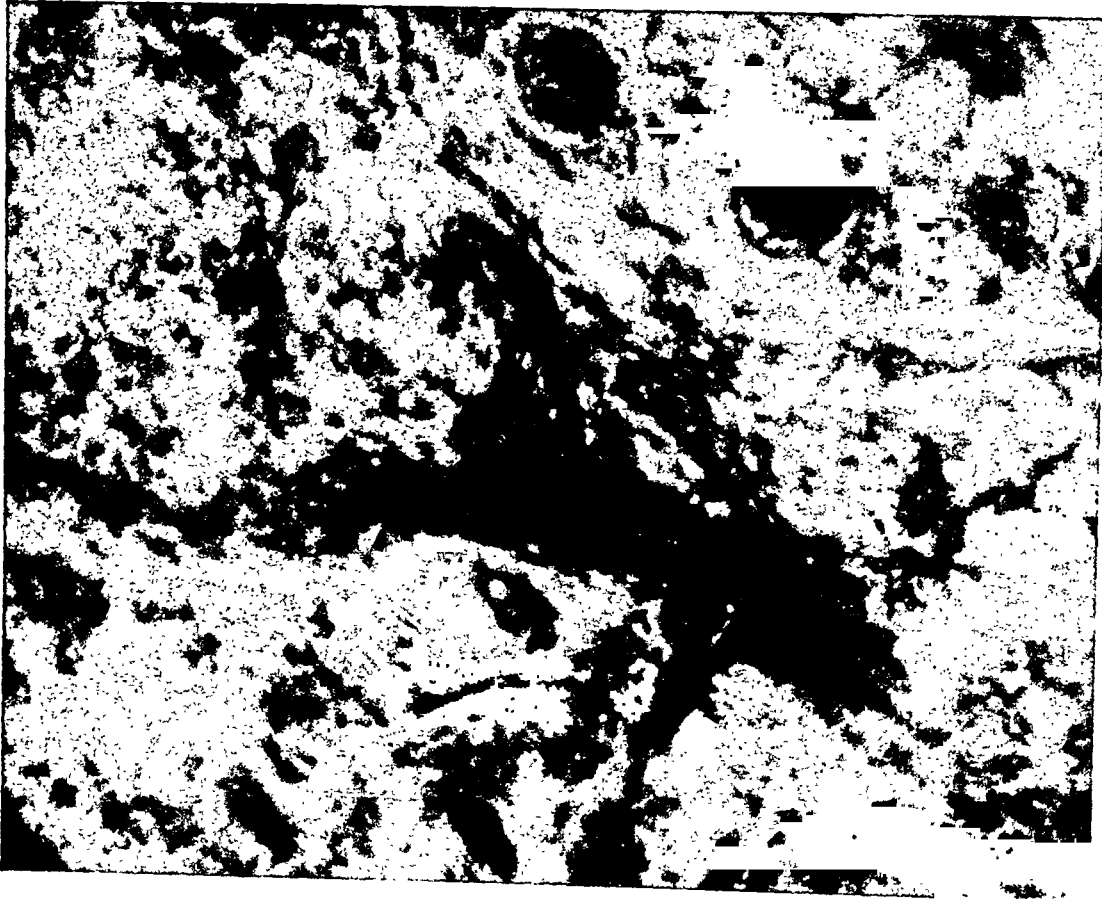
FIG. 1. Nervous plexus of the afferent arteriole near the capsular junction. The lower left branch accompanies the afferent arteriole. Various nerves arise from the plexus and one nerve ending is seen in contact with a cell of the pre-glomerular apparatus. $\times 1100$.

FIG. 2. Photomicrograph of the same plexus. $\times 1225$.

1



2



Oberling

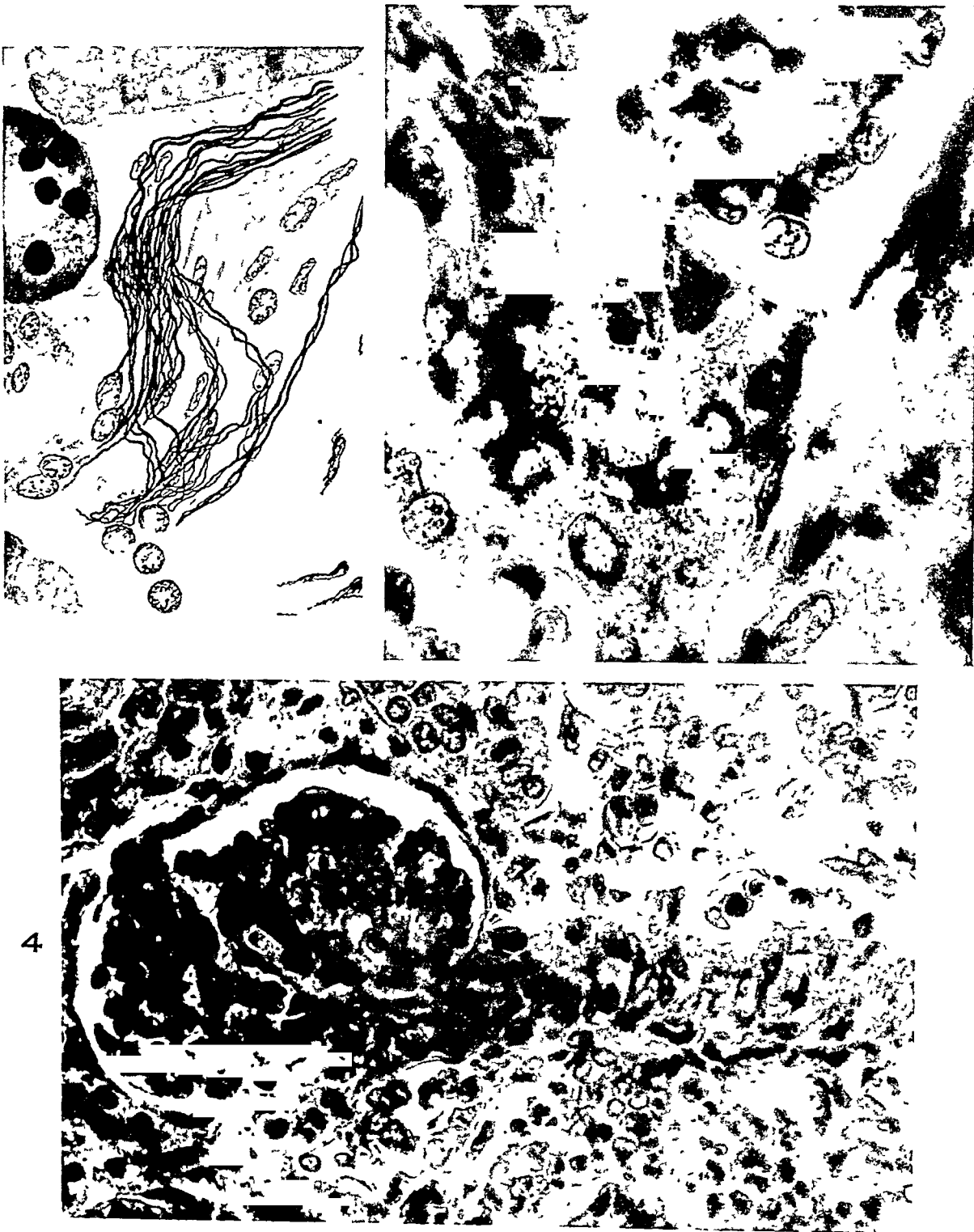
Preglomerular Cellular Apparatus

PLATE 29

FIG. 3. Another view of a preglomerular nervous plexus. The lateral branch is here much smaller than in Figure 2. $\times 745$.

FIG. 4. Preglomerular apparatus in a kidney of a child, 8 weeks old. The afferent arteriole runs in a straight line towards the glomerulus. Near the capsular junction the vessel shows the typical modification of its wall characterized by the presence of large cells. $\times 330$.

FIG. 5. Preglomerular apparatus in the same kidney. At this magnification the granular cells surrounding the afferent arteriole appear very distinctly. $\times 830$.



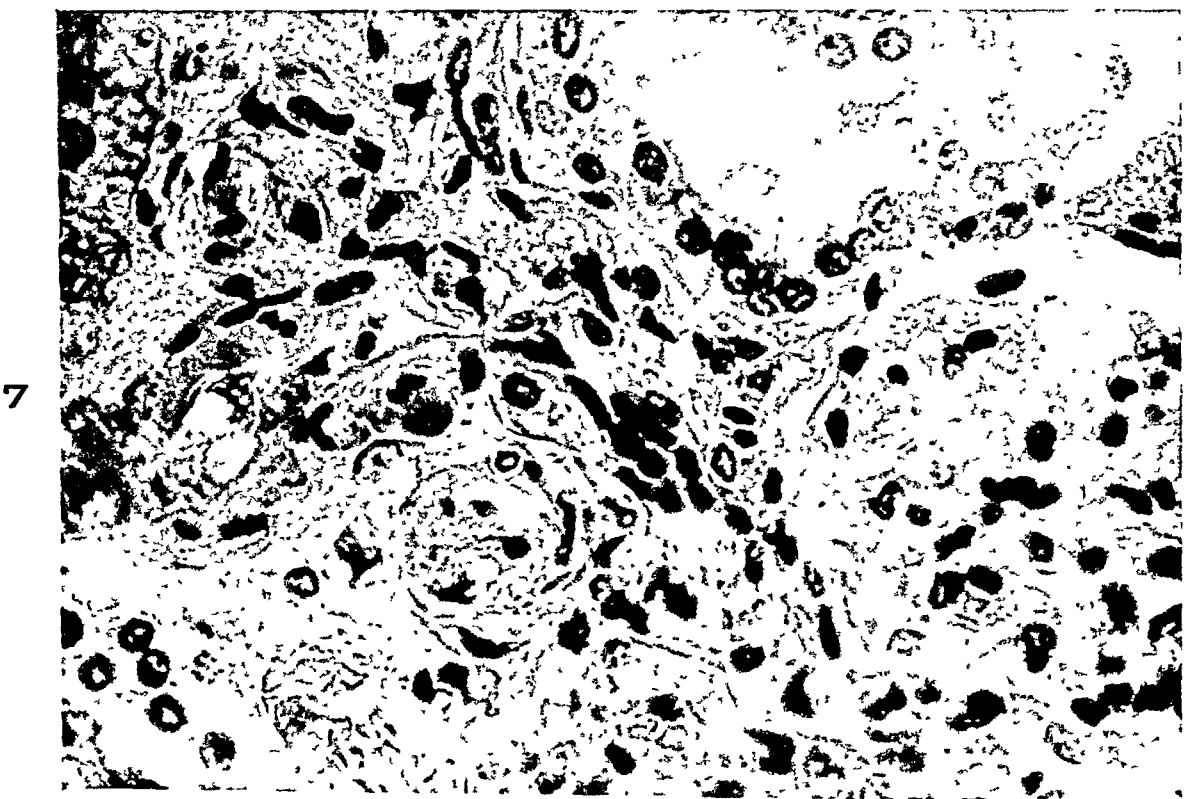
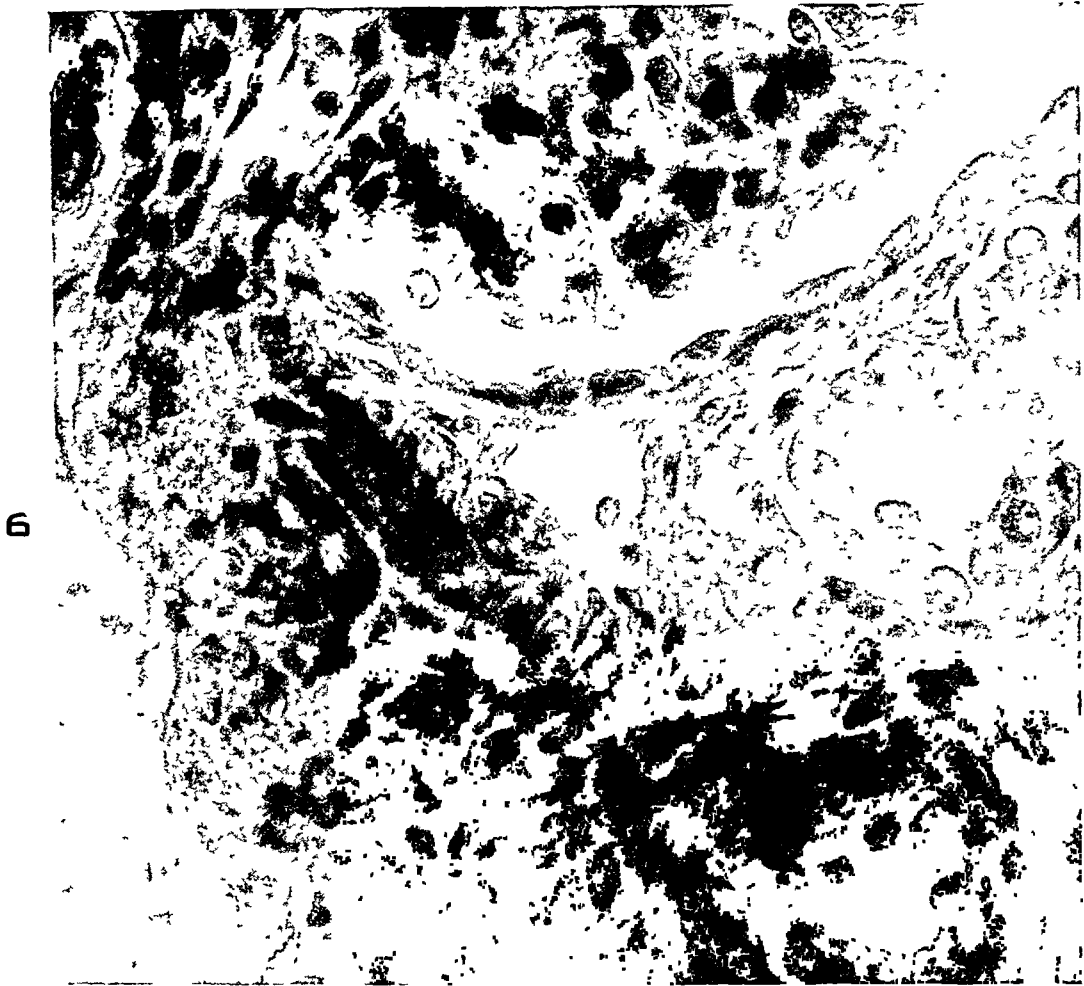
Oberling

Preglomerular Cellular Apparatus

PLATE 30

FIG. 6. Normal kidney of a 24-year-old male. Glomus-like structure around the bifurcation of the afferent arteriole and Isaac-Ludwig's arteriole. The latter is seen branching to the left. $\times 570$.

FIG. 7. White male, 50 years of age; hypertension for many years; died of apoplexy. The photomicrograph shows the afferent arteriole and Isaac-Ludwig's arteriole with hyaline degeneration of their walls. The preglomerular apparatus located near the capsular junction in contact with the macula densa shows retracted and vacuolar cells with pyknotic nuclei. Frozen sections from this case, stained with scarlet red, show marked fat infiltration of the preglomerular cells. $\times 570$.



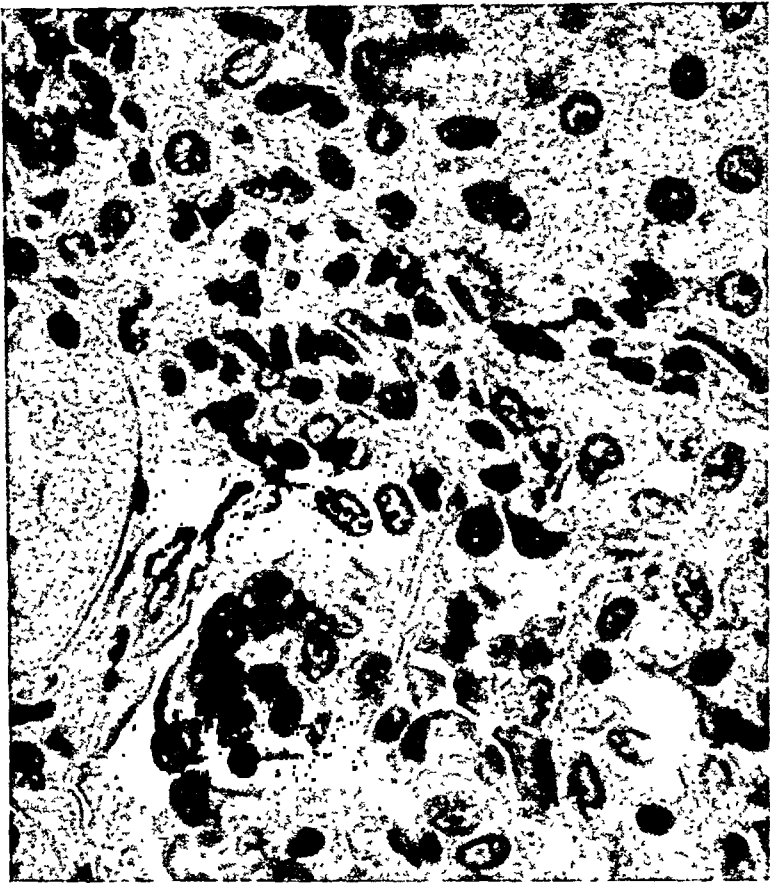
Oberling

Preglomerular Cellular Apparatus

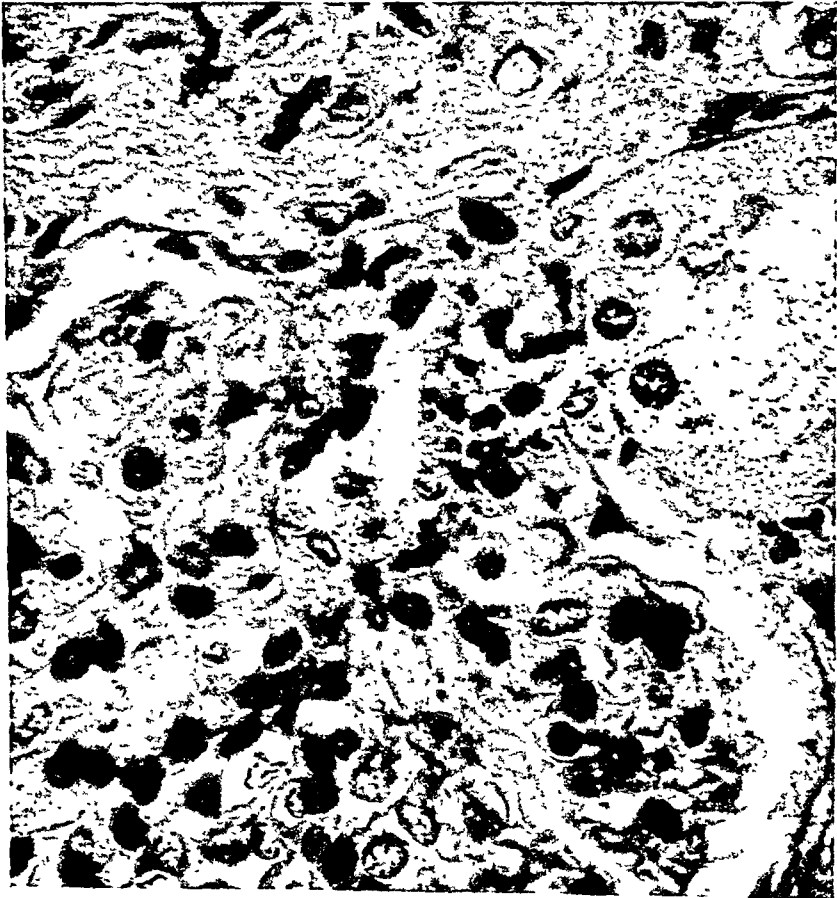
PLATE 31

FIGS. 8 and 9. White female, 65 years old; obesity; hypertension; died of cardiac insufficiency. Pronounced degenerative lesions of all the preglomerular cells which present pyknotic nuclei and a homogeneous or vacuolar cytoplasm. $\times 600$.

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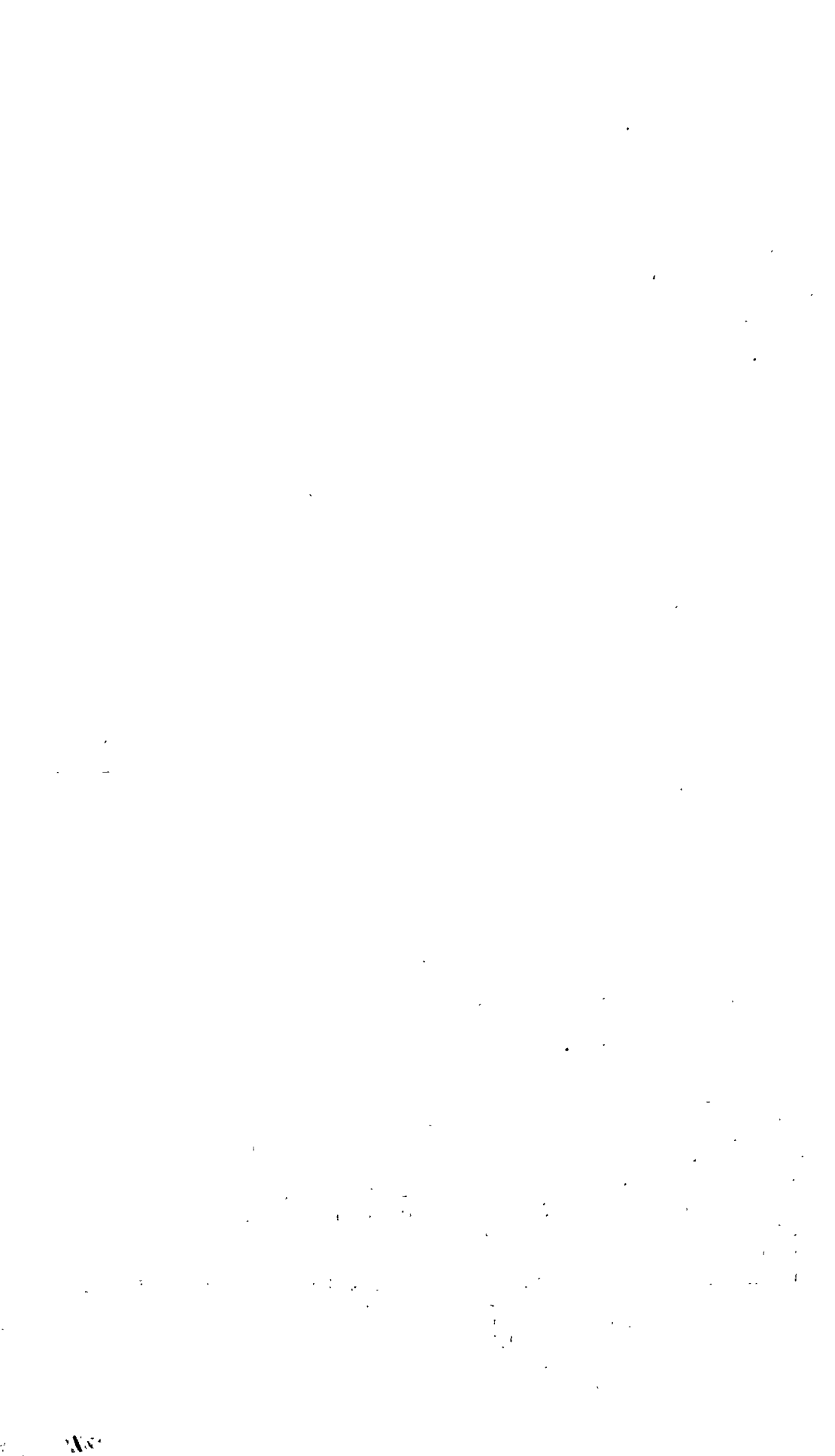


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GENERALIZED VACCINIA WITH DUAL VIRUS INFECTION

A CASE REPORT *

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Dual or multiple virus infections have been demonstrated experimentally¹⁻³ by inoculation of known viruses in appropriate animals. Different varieties of specific inclusion bodies have been seen³ in an individual host cell. Certain virus infections appear to maintain their usual characteristics in the presence of another virus while other dual or mixed virus infections exert an interference phenomenon.⁴

This preliminary report concerns the demonstration of both cytoplasmic and intranuclear inclusions in material obtained from a clinical case of generalized vaccinia.

REPORT OF CASE

J. R. (B.C.H. no. 100152), a white male infant, 1 year of age, the youngest of three siblings, was admitted to the Boston City Hospital on July 6, 1941, with a generalized skin eruption and high fever.

Ten days before admission the patient and a 4-year-old sister were vaccinated by the epidermal scratch method. The sister followed the ordinary course of vaccinia. Six days after vaccination, the patient had a temperature of 104°F. and a vesicle appeared at the site of vaccination. Within a few hours, other vesicles appeared around the vaccination site. The following day, vesicles were observed over the entire left arm and 2 days later, or 9 days after the vaccination, numerous vesicles were present over the legs, arms, face and axillae. A persistent cough developed simultaneously with the first appearance of the vesicles.

The family history was not contributory.

The patient had been bottle fed since birth. His development and general health were considered good. At the age of 2 months he had had pertussis which was followed by two bouts of bronchopneumonia, the second attack being 8 months prior to the present illness. Recovery was complete. Recurrent eczema had been present since the age of 3 months but none was present at the time of vaccination. He was found to be sensitive to string beans, tomatoes, spinach, eggs, oranges, and wheat.

Physical examination revealed a critically ill, dehydrated, well developed and well nourished, mentally alert male infant, with a temperature of 104°F., a pulse rate of 152 beats per minute and a respiration rate of 50 per minute. Breathing was rapid and grunting. Over both arms were many discrete and confluent, round, shotty, umbilicated pustules. Similar semiconfluent umbilicated pustules were present on the legs in great numbers, and a few were scattered over the skin of the face, neck, axillae, anterior chest and abdomen. All lesions were fundamentally of identical appearance. No lesions were present on the palms, soles, or oral mucosa. There was moderate enlargement of the cervical and right inguinal lymph nodes. The nodes of the left axilla were markedly increased in size. There was slightly impaired resonance over the left upper chest with coarse bronchovesicular breathing and rare

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moist râles. Edema of a moderate degree was present in both arms. There were no other positive physical signs.

The urine was essentially negative. The blood cell counts were within normal limits and the Hinton test on the blood was negative. Hemolytic *Staphylococcus aureus* was cultured from the pustules.

Course. Fluids were given by mouth. Sulfathiazole, grains $7\frac{1}{2}$ (0.5 gm.), was given every 4 hours for 6 days. The skin lesions were treated with a 1:10 solution of chlorated soda, and powdered zinc stearate.

The temperature rose to 106.2°F. (rectal) 2 days after admission and a generalized convulsion ensued. Cold sponge baths reduced the temperature and the patient improved. Several convulsions occurred during the course of the illness, when the temperature became 104°F. or higher. Occasionally the patient became cyanotic, necessitating oxygen therapy. The signs of bronchopneumonia rapidly disappeared. The pustular lesions crusted slowly, finally healing with only slight residual scarring. The patient was discharged entirely well 38 days after admission to the hospital.

Experimental Procedures

Scrapings from the pustular skin lesions 12 days after the first appearance of the generalized skin eruption were inoculated on the corneas of a fully grown female and a male rabbit. Each testicle of the male rabbit was inoculated with 0.1 cc. of a saline suspension of the initial scrapings. The female rabbit was sacrificed after 96 hours, the male after 124 hours. Exudate and small, raised areas suggestive of vesicles appeared over the corneas and conjunctivae of both animals in 72 hours, reaching a maximum in 96 hours. The testicles became firm in 72 hours, reaching a maximum induration in 96 hours. The rectal temperatures of the rabbits varied from 105° F. at 72 hours to 103° F. in 96 hours. The temperature of the male rabbit returned to normal within 120 hours.

Portions of each eye and testicle were removed from the sacrificed animals immediately after death and fixed in Zenker's solution. Histological sections were stained with the phloxine and methylene blue stain. Portions of each eye and testicle were also saved fresh for transfer.

Microscopically, the corneal lesions were consistent with lesions produced by vaccinia alone. There was marked ulceration of the cornea with an acute inflammatory reaction consisting of polymorphonuclear leukocytes, macrophages and strands of fibrin. About the periphery of the ulceration the majority of the epithelial cells contained cytoplasmic inclusions which were typical of Guarnieri's bodies of vaccinia.

In addition to the cytoplasmic inclusions, intranuclear inclusions were present. These were few in any one lesion of the cornea or testicle. Stained with phloxine and methylene blue, they appeared as homogeneous, brilliant pink masses pushing the nuclear chromatin toward the nuclear membranes, producing a margination of the nuclear

chromatin about the masses. The intranuclear and cytoplasmic inclusions, as far as could be determined, were present only in epithelial cells. In rare instances intranuclear and cytoplasmic inclusions were present in the same cell.

Part of the fresh cornea of the female rabbit originally inoculated was finely ground and suspended in physiological saline solution and inoculated on the cornea of a second anesthetized rabbit and so on through thirty-nine consecutive transfers. It was thought best not to use testicular material or continue testicular inoculation for fear of introducing Virus III into an already complicated picture.

The intranuclear inclusions continued to appear in approximately the same numbers as in the original inoculation. The cytoplasmic inclusions were usually numerous.

Since the inclusions of vaccinia are only cytoplasmic, it follows that either two viruses were responsible for the lesions or that one virus producing both cytoplasmic and intranuclear inclusions was being transmitted. Variola characteristically produces both cytoplasmic and intranuclear inclusions in man but it has been shown⁵ that material obtained from variola lesions and inoculated on a rabbit's cornea produces lesions identical with vaccinia; that is, the specific cytoplasmic inclusions of vaccinia.

Paravaccinia is also characterized by cytoplasmic and intranuclear inclusions but can be excluded, as man is the only known susceptible host.⁶

On the assumption that I was dealing with a dual virus infection, attempts were made to separate the virus producing intranuclear inclusions from that causing the cytoplasmic inclusion. Five rabbits were immunized with a stock vaccine virus. Nineteen days later one was inoculated on the cornea with a suspension of the cornea from the early rabbit passage and subsequent consecutive transfers were carried through the immunized rabbits. The cytoplasmic inclusions of vaccinia as well as the unknown intranuclear inclusions failed to appear. It was impossible to demonstrate intranuclear inclusions in the absence of the cytoplasmic inclusions in any of the rabbits immunized. Control or nonimmunized rabbits inoculated with the same suspension showed both the cytoplasmic inclusions of vaccinia and the unidentified intranuclear inclusions.

The possibility that the intranuclear inclusions might be those of herpes was investigated. Three rabbits were inoculated intracerebrally with a saline suspension of finely ground corneal lesions, but these failed to show any characteristic of herpes encephalitis nor were lesions demonstrable histologically. It is interesting to note that recently

Anderson³ inoculated herpes simplex and vaccinia virus on the chorioallantois of chick embryos, producing dual infections. Doubly infected cells occurred but rarely and only in areas of the epithelium where vaccinia infection merged into foci which were purely herpetic.

The viruses of varicella and herpes zoster are characterized by producing only intranuclear inclusions. Both can be excluded as only possibilities for as yet it remains to be demonstrated conclusively that either can be transmitted to animals.

The question arises whether Virus III might have been present in the two rabbits originally inoculated and have been repeatedly transferred through thirty-nine transfers. If such were the case it is to be expected that by repeated transfers the Virus III would become more prominent and readily transferred to rabbits immune to vaccinia, but this did not occur in our experiments.

The chorioallantois of 12- to 14-day-old chick embryos was employed in an attempt to accentuate the growth of the intranuclear inclusions. However, the cytoplasmic inclusions so overshadowed the intranuclear inclusions as to make their identification extremely difficult. Emulsions of previously inoculated chorioallantoic membranes were inoculated on the corneas of rabbits but with no significant increase in the number of intranuclear inclusions over rabbit cornea-to-cornea transfers.

Guinea-pigs were employed as experimental hosts through seven consecutive transfers. The virus was inoculated on the cornea. In no case were intranuclear inclusions found, while cytoplasmic inclusions were numerous.

Six white mice were inoculated intraperitoneally and intracerebrally with saline suspensions of rabbit corneal lesions. No untoward reactions resulted and histological examination failed to reveal inclusions of any sort in the brains or in the viscera.

The conclusion therefore was reached that the intranuclear inclusions may represent a new virus or a known virus so altered by the symbiotic presence or interference phenomenon of vaccinia as to render it difficult to identify. It is possible that the original vaccine given the patient was contaminated by another virus. Unfortunately, it was impossible to study the original vaccine. It is also possible that the patient was harboring a virus which was activated by the vaccination. It is recognized that generalized vaccinia is most apt to occur in persons susceptible to eczema or other dermatological disorders. Since I did not have the patient's skin lesions available for biopsy, the possibility of pre-existing virus infection cannot be determined.

SUMMARY

Cytoplasmic and intranuclear inclusions were demonstrated by inoculation of material from a case of generalized vaccinia into animals. The cytoplasmic inclusions were identified as vaccinia but the intranuclear inclusions were not identified. The intranuclear inclusions failed to appear in the absence of vaccinia although in combination the two viruses were readily transmitted through thirty-nine consecutive rabbit transfers. The virus producing the intranuclear inclusions did not behave in experimental animals in a manner characteristic of known viruses producing intranuclear inclusions.

I wish to express my appreciation to Dr. Frederic Parker, Jr., and to Dr. James R. Dawson, Jr., for valuable suggestions and assistance in the preparation of this paper.

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OBSERVATIONS ON THE STRUCTURE OF BONE IN ESTROGEN-TREATED COCKS AND DRAKES *

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Among the many hormones which influence the finer structure of bone, estrogens have, during the past several years, attracted particular attention, and it is now well established that experimental treatment may lead to profound modifications in the internal configuration of bones. Rats,¹⁻⁸ mice,⁹⁻¹⁴ guinea-pigs,^{3-5, 13, 15, 16} chickens,^{8, 17} ducks,¹⁸ pigeons¹⁹⁻²¹ and sparrows,^{22, 23} all show these effects, although the amount of response varies from one species to another and also with sex, age and other intrinsic factors.

A number of investigators have studied the histologic consequences of estrogen treatment on bone, especially on the long bones of young and growing mammals. The present report is concerned with observations on long bones of estrogen-treated cocks and drakes, and particularly with estrogen-mediated changes in the bones of mature birds.

Information concerning the animals which were used in this work and the doses of hormone which were injected is contained in previous publications.^{8, 17, 18} Briefly, the work of one of us (B. Z.) was done with White Leghorn cockerels which were 6 weeks of age when treatment was started, while the experimental material of the other (W. L.) consisted of mature White Leghorn and Creeper cocks and of mature Pekin and Mallard drakes. The hormone used was estradiol benzoate. For details concerning duration of treatment and dosage we refer to our earlier publications.

ROENTGENOGRAPHIC OBSERVATIONS

Young Cockerels

X-ray pictures of the femur and tibia were taken, at the time of autopsy, of those cockerels which had been treated with estrogen after reaching the age of 6 weeks. Drastic changes occurred in some of these animals. After prolonged treatment the long bones failed to attain their normal length, with a tendency for the tibia to be relatively shorter than the femur. The earliest roentgenographic signs of bone changes were visible in a cockerel which had, during 21 days, received injections of 5 mg. of estradiol benzoate three times a week. There was a diffuse increase in density in the shaft and in the epiphyseal ends of the femur

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and, to a lesser degree, in the tibia. In the metaphyseal regions the changes were less uniform; there were scattered islands of particularly dense bone. In another cockerel treated similarly, but for 5 weeks, bone density was still further increased (Fig. 1). In yet other cases, treated for longer periods, the bones were very irregular in density. There were indications of the removal of bone salts from the epiphyseal region and from the shaft, but there were also, scattered throughout the shaft, islands of very dense bone (Fig. 2). In extreme cases, after long-continued treatment, only traces of the marrow cavity remained in the femur (Fig. 3).

Of the estrogen-treated adult cocks, roentgenograms were taken of only the humerus, ulna, radius and tarsometatarsus. No modifications due to treatment could be seen in these bones.

Ducks

In the humerus of adult Mallard drakes no response to estrogen treatment was visible in roentgenograms. In mature Pekin drakes, on the other hand, a slight and diffuse increase of density was noticeable in the distal half of the shaft. This was most pronounced in the animal which had received the largest amount of estrogen.

As in cocks, the femora of drakes responded more to estrogen administration than any other long bone. In Mallard drakes the roentgenograms indicated but slight changes in the structure of the femur. In the most advanced cases (highest dose of estrogen) there was a diffuse increase of bone density, especially in the central section of the shaft and near the joint surfaces. In contrast to this, the femora of Pekin drakes had undergone extreme changes under the influence of estrogen administration, and these changes showed a definite relationship to the dosage of hormone which was employed (Fig. 4). Density of the bone shadows was much increased and in the most extreme case (drake P₅) the marrow cavity appeared nearly obliterated. Formation of new bone was greatest at the epiphyseal ends, where normally the number of endosteal trabeculae is largest, and, vice versa, the least increase in bone deposition occurred where the fewest trabeculae are normally present, *viz.*, in the middle part of the diaphysis.

No radiographic changes could be seen in the tibia of Mallard drakes; but, in the Pekin drakes the modifications of tibial structure were conspicuous. With the lowest dosage of estrogen (drake P₁) bone density was increased chiefly in the region of the proximal epiphysis and metaphysis and to a lesser degree along the inner surface of the shaft. In addition to these modifications there were, after greater hormone dosage, many small localized areas of increased density throughout the

upper half of the tibial diaphysis. The lower part of the tibial shaft and the distal epiphyseal region appeared nearly or entirely free of changes (Fig. 5).

No radiographic signs of estrogen effects could be seen in the tarsometatarsal bones of either Mallard or Pekin drakes.

GROSS OBSERVATIONS

The following observations relate to long bones, of mature experimental and control animals, after they had been sawed in half frontally, cleaned, bleached and defatted.

Cocks

After relatively low doses of estrogen (total of 1.5 to 2 mg. in 27 days) the long leg bones of four adult cocks showed no macroscopic changes. In another group of four cocks which had been injected with 7 to 9 mg. of estrogen in the course of 2 months the responses were definite. In the femur the inner surface of the shaft and all endosteal trabeculae were covered by a thin layer of new bone. The same, though to a lesser extent, was true for the tibia, except that the distal metaphysis and epiphysis were free of new bone deposits. The tarsometatarsus showed no reaction at any dosage level. In two capons which were treated with somewhat larger doses (11.5 and 12.5 mg. of estrogen, respectively, during 2 months) the changes were about the same as those in the last group, except that there was a more uniform response throughout the whole length of the tibia. The results again were similar after still greater amounts of estrogen, administered during shorter or longer intervals. Within certain limits the osseous changes increased in extent *pari passu* with the amount of estrogen which had been given. The imprint of high doses of estrogen on bone structure may, however, be less extensive than that of smaller doses. This is illustrated by the following examples. In a group of four cocks which received 2 mg. of estrogen daily for 12 and 19 days, respectively, the two which had been treated for 19 days showed definitely less new bone than the animals which had been injected for only 12 days. Again, in a group of three cocks, one received 31 mg. of estrogen in the course of 130 days and another cock was injected with only 23 mg. during the same period. The changes were less pronounced in the former animal than in the latter. Both of these cocks showed less new bone than the third one which was given 7 mg. during 20 days. There is evidence indicating that these results are due to secondary resorption of newly-formed bone.

Ducks

Gross inspection of the long bones of estrogen-treated mature Mallard drakes showed that the changes in the interior structure of bone are less pronounced than in cocks. No indications of response could be seen in the humerus. As far as the long bones of the leg are concerned, the femur reacted most intensely, the tibia less, the tarsometatarsus little, if at all. Within the femur, about equal amounts of new bone were formed in the proximal and distal ends, but much less in the middle part of the diaphysis. It should be emphasized, however, that there was some measure of response in the central section of the shaft. Since this region is, normally, entirely free of trabecular bone, it is clear that estrogen-induced bone formation can occur in the absence of pre-existing endosteal trabeculae. The proximal end of the tibia of Mallards undergoes drastic changes under the influence of estrogen; the effect becomes less conspicuous in the upper half of the shaft and is lacking entirely in the lower third of the diaphysis and in the distal head of the bone.

In Pekin drakes the osseous responses to estrogen were much more extreme than in either Mallards or cocks. There were no grossly visible changes of the humerus. The leg bones showed the same proximo-distal response gradient as that observed in Mallards and cocks, *viz.*, femur > tibia > tarsometatarsus. This sequence holds at all dosage levels. Complete obliteration of the marrow cavity of the femur occurred in extreme cases. The distal end of the femur tended to undergo somewhat more extreme hyperossification than the proximal one, and the central parts of the diaphysis showed gross reactions only to high doses of hormone. In the tibia the proximal end was the most responsive region of the bone; the upper end of the diaphysis followed next; in the lower part of the shaft hyperossification was slight, and was absent in the distal head. There were no grossly observable changes of the tarsometatarsus even at the maximum amounts of estrogen used in our experiments.

Under the influence of the lowest doses of estrogen some trabeculae disappeared from the central part of the diaphyseal shafts of femur and tibia, while simultaneously definite hyperossification took place in other parts of the same bones. Evidence of halisteresis was found also in the tarsometatarsus in which there was no evidence of hyperossification elsewhere.

A comparison of bones from untreated mature animals revealed that femora and tibiae of Mallard drakes have fewer endosteal trabeculae than the same bones of cocks. The reverse, *viz.*, a much greater amount of spongiosa, was found in femora and tibiae of normal Pekin drakes

than in the corresponding bones of either Mallards or cocks. This sequence coincides with that of the degree of response after estrogen treatment, *viz.*, Mallards < cocks < Pekins. A similar relationship exists with regard to different parts of one and the same bone; for instance, there is less (and coarser) spongiosa in the central section of the femoral diaphysis than in other parts and this region is the least responsive.

In a general way, the degree of hyperossification of femur and tibia was the greater the higher had been the amounts of injected estrogen (duration of treatment being the same). In the Mallard and Pekin drakes the results from the highest dosage level of our tests, 1 mg. daily for 3 weeks, appeared to approach the maximum response obtainable; for the effect of 1 mg. daily was not much greater, with regard to degree of hyperossification, than that of 0.5 mg. per day.

HISTOLOGIC OBSERVATIONS *

Cocks

Following the lowest dose of estrogen which we gave to adult cocks (nos. 5646 and 3973, 0.17 to 0.23 mg. of estradiol benzoate daily for 4 weeks) the outstanding feature of the long bones was destruction and resorption of bone. This was most marked in the femur (Fig. 6), less so in the tibia, and least in the tarsometatarsus. There was slight thinning of the femoral and tibial shafts; the periosteal bone showed splotchy staining; many haversian canals had an increased diameter and their number was greater than normal; the borders of the haversian canals frequently had a frayed appearance and accumulations of detritus could be seen; there were Volkmann's canals and cavities containing osteoclasts. Vascularization was increased. In some regions, especially in the distal end of the femur, the processes of bone reconstruction extended to the endosteal trabeculae. In the marrow cavity the lymphocytes were often replaced, to a greater or lesser extent, by pseudo-eosinophils; in other places the reverse was true. There was some evidence of fibrosis of the marrow but this did not assume extensive proportions. In a few places the inner surface of the shaft and the trabeculae which project into the marrow cavity were covered with uncalcified osteoid tissue and there were a few newly-formed endosteal spicules. The number of osteoblasts was increased on the surface of the old and of the more recently formed bone. On the whole, however, there was more evidence of bone destruction or resorption than of formation of new bone.

* The bones were fixed in formaldehyde. For staining we used chiefly Dominici's orange-eosin-toluidin blue method (Romeis, B. Taschenbuch der mikroskopischen Technik. R. Oldenbourg, Munich & Berlin, 1924, ed. 11, p. 140).

As one progresses to animals which had received higher doses of estrogen the signs of bone destruction become less prominent, whereas those of new bone formation increase in conspicuousness. Heightened vascularization was always evident. Fibrous degeneration of marrow, disintegration of marrow cells and accumulations of cell fragments (*i.e.*, focal necrosis) could be seen everywhere. The fibrous degeneration seemed to involve the pseudo-eosinophils more than other cell types. There was evidence of the transformation of small lymphocytes into osteoblast-like cells and finally into bone cells. Considerable amounts of osteoid tissue, in various stages of calcification, could be seen. New endosteal trabeculae appeared along the surface of the marrow cavity and also between old bone spicules. Marrow degeneration and new bone were also found in osseous cavities of the shaft itself (Fig. 7).

In the two cocks which had received the highest doses of estrogen (nos. 97 and 99, 2 mg. of estradiol benzoate daily for 19 days) the extent of the changes in the femur and tibia resembled that in Pekin drakes which had received about half that amount (to be discussed later in this paper). There were many new endosteal trabeculae in the shafts of both bones, but especially in that of the femur. The marrow showed extreme fibrous degeneration and much cell-free granular debris near the newly calcified bone spicules. Vascularization was greatly increased and there were definite signs of thickening of the walls of small blood vessels and of stasis. There were also accumulations of plasma (containing some red cells) outside of the vessels.

Fibrous degeneration of marrow and small amounts of new bone were also observed in the mural osseous cavities of the tarsometatarsal shaft, but not in the marrow cavity of this bone (Fig. 8). The haversian canals of the tarsometatarsus were much enlarged in diameter.

As in the material from ducks, the pseudo-eosinophils were particularly subject to fibrous replacement, whereas the lymphocytes participated to a much less degree in this process. There were large numbers of small lymphocytes in the center of the marrow cavity and some of these were in transition to water-clear osteoblast-like cells which were obviously destined to become bone cells. There was no osteoclastic activity in the bones with most extreme changes.

In young cockerels treated with estrogen the types of reactions and the sequences of events were very similar to those described for mature animals. The extent of response, however, was much greater, and, in extreme cases, led to nearly complete obliteration of the marrow cavity (femur) by newly-formed bone (Fig. 9).

As in the material already described, the first response of the long

bones to estrogen appeared to be increased vascularization, followed by widening of the haversian canals in the shaft, disappearance of fat from the marrow cavity, multiplication of marrow cells, fibrous degeneration of marrow, circulatory stasis and extravasations, production of hyalin from erythroblasts and red cells of the marrow, and finally the formation of new bone (Figs. 10 and 11). All these changes proceeded more rapidly in the femur than in the tibia.

Control animals injected with cholesterol showed increased vascularization and some signs of circulatory stasis and hyaline formation, but no other changes. Control animals which had received injections of olive oil had an increased blood supply to the marrow cavity, but there were no other bone abnormalities.

Pekin Drakes

The bones of estrogen-treated Pekin drakes showed two outstanding features, *viz.*, marrow fibrosis and formation of new bone trabeculae (Fig. 12). These and other processes varied in extent according to the particular region and according to the amount of estrogen which had been injected.

In the drake which had received the lowest dose of estrogen (P_1) there was great distention of the capillaries and blood spaces. All marrow cells were much increased in number, and this increase followed the pattern of normal distribution, *i.e.*, in any particular bone region the normal proportions of different cell types seemed to be more or less preserved. Thus, it was observed that in the proximal tibia of control animals pseudo-eosinophils were found almost exclusively near the endosteal surface of the metaphysis, whereas myelocytes became more and more frequent toward the center of the bone. On the other hand, the predominance of myelocytes in the center of the joint end (in control animals) gradually disappeared toward the shaft, and in the middle region of the diaphysis few cells other than pseudo-eosinophils were present. This order of distribution of different cell types was not affected by the multiplication of cells occurring under the influence of estrogen. Fatty marrow, common in the controls, was much reduced or absent in the treated animals.

Another relationship between normal structure and degree of response to estrogen treatment could be observed in cross sections of the tibial shaft. In normal ducks and domestic fowls the large osseous cavities (Resorptionshöhlen or Bauplätze of Petersen ²⁴) are restricted to the fibular side of the tibial shaft. Red marrow is formed within the osseous cavities and also along the fibular surface of the marrow cavity, whereas the remainder of the marrow cavity, in adult birds, contains fatty marrow. This structural asymmetry was reflected in the changes

caused by estrogen treatment. Within the osseous cavities of the shaft fibrosis of the marrow was more extreme than elsewhere, and in the marrow cavity more new bone was formed in the fibular part than in the remainder (Fig. 14). If much new bone was present, the higher rate of bone formation on the fibular side of the tibia became especially noticeable by a column of spongiosa bulging, on this side, into the marrow cavity. Again, the occurrence of abnormal arterioles was much more common on the fibular side of the tibia than in other parts.

In the bones of treated animals there was evidence of fibrotic replacement of myelocytes and of pseudo-eosinophils. This marrow fibrosis was the more marked the higher had been the amount of injected estrogen. In extreme cases very little normal marrow appeared to remain (Fig. 15). In some places one could see relatively large amounts of cell-free substance, thus produced. Elsewhere these accumulations were interspersed with smaller or larger numbers of osteoblast-like cells.

On the bony surface of the marrow cavity and along the surface of endosteal trabeculae newly-formed bone was present. The amount of new bone varied with the amount of estrogen which the particular animal had received. In the more extreme cases many trabeculae consisting entirely of new bone were present. They were usually composed of irregular, concentric layers of new bone structure.

These new bone trabeculae were generally, but not invariably, covered with a thin layer of degenerated marrow containing osteoblast-like cells. Fibrous marrow degeneration was especially evident in the vicinity of bone trabeculae. Various stages of calcification of fibrous marrow could be seen.

Multinucleated giant cells (osteoclasts) were numerous along the surface of some of the new bone trabeculae, but only a few were found near others (Fig. 16).

A feature observed only in the animals which had received the largest amounts of estrogen was the occurrence of cartilage within the old endosteal bone (Fig. 17). Some bone trabeculae showed definite signs of halisteresis in the central parts. This seemed to be followed by the appearance of small areas of cartilage. In the more extreme cases only a narrow border of the old bone remained on the surface of a trabecula, the interior having been transformed entirely into large-celled cartilage. All the cartilage cells were oriented at right angles to the long axis of the trabeculae. Another peculiarity which was restricted to birds with the highest dosage levels was the presence of "cysts" in the marrow cavity. These "cysts" had a lining consisting of one layer of cells and presumably represented sections through greatly dilated venules. They were filled with large masses of erythrocytes, with eryth-

rocytes and plasma, or almost exclusively with plasma and but a few red cells. Further signs of stasis were found in many capillaries and venules (Fig. 19). Accumulations of plasma occurred frequently (Figs. 13 and 18) and the arteriolar walls often showed definite hypertrophy of the elastic elements of the media and a relative reduction in the width of the vessel lumen. An increase in vascularization and widening of the capillary lumina was observed in the bone marrow of those animals which had received the lower estrogen doses. This increase in blood supply appeared to be secondary to degenerative changes of the marrow; for cross sections of the diaphysis (femur, tibia), after low and medium doses of estrogen, demonstrated the presence of all structural alterations (marrow fibrosis, increased vascularity, new trabecular bone) in the peripheral parts of the original marrow cavity, whereas the only changes which were noticeable in the center relate to the large lymphocytes which had indistinct nuclei and a slightly acidophilic instead of a basophilic staining quality of the cytoplasm. On the other hand, in animals which had received high doses of estrogen the changes which, on the lower hormone levels were confined to the periphery, extended to the center of the marrow cavity. Accumulations of plasma were also frequently observed outside of vessels.

No indication of new bone formation was found in the humerus of estrogen-treated animals, but there was destruction of old bone throughout the humeral shaft (Fig. 20). There were new Volkmann's canals and alongside them one could observe accumulations of irregular-sized granules of broken-down bone. Disintegration and resorption of bone (osteolysis) could, however, be seen throughout the shaft, independent of the presence of haversian or Volkmann's canals. There were no osteoclasts. Vascularization was increased.

The histologic structure of the tarsometatarsus resembled that of the humerus. As in the humerus, there was evidence of destruction of old bone and there were numerous Volkmann's canals. There were no white cells in the marrow cavity of either treated or control animals, and there was no indication of the formation of new bone. Within the bony cavities of the shaft, however, small numbers of marrow cells were present. These marrow cells often were in the process of fibrous replacement and thin layers of new bone were found here and there covering the walls of these cavities.

Mallard Drakes

The histologic changes which estrogen produced in the bones of Mallard drakes were in principle the same as those found in Pekin drakes, but were much less extreme. They include increased vasculari-

zation, signs of stasis, marrow fibrosis, appearance of new endosteal bone spicules, and the presence of osteoclasts.

The long bones of control Mallards differed markedly in histologic structure from those of control Pekins. There was much less spongiosa in the Mallard bones, and the number of white cells in the marrow cavity was much lower than in Pekin drakes. As will become clear from our subsequent discussion, the relative scarcity of lymphocytes and pseudo-eosinophils probably had a direct bearing on the lesser response of the Mallard bones to estrogen.

The number of pseudo-eosinophile cells in the marrow was much increased in the animals which had been given the lowest dose of estrogen, but this increase became less conspicuous with increasing amounts of injected hormone. The opposite appeared to be true in regard to the large lymphocytes, *i.e.*, their number was more definitely above normal the more estrogen the animal had received. The multiplication in number of large lymphocytes occurred predominantly along the surface of capillaries where large accumulations of them were found frequently. Some of these cells stained only faintly. There seemed to be transitional stages from these poorly staining lymphocytes to the clear osteoblast-like cells which covered the newly formed bone.

Vascularization of the bones was greatly increased in estrogen-treated Mallards, both the number of capillaries and their lumina being enlarged. In contradistinction to the Pekin drakes, there was little evidence of fibrous degeneration of marrow in the long bones of Mallards, except in those animals which received the highest doses of estrogen.

No evidence of hyperossification was found in the tarsometatarsus. No white cells were observed in the marrow cavity of this bone in either control or treated animals.

There was definite evidence of halisteresis in the tarsometatarsal shaft of treated animals, especially around the haversian canals. The lumina of the haversian canals frequently appeared enlarged. No osteoclasts were present. Bone destruction was observed also in the shaft of other long bones. For instance, there were many Volkmann's canals in the femoral shaft of the Mallard drake which had been treated with the largest amount of estrogen.

DISCUSSION

It can be concluded from our observations that the principal effects of estrogen treatment, as far as bone structure is concerned, are of a similar nature in young and adult cocks and in drakes, although the degree of change varied widely in the different forms which were studied.

For the purposes of the present discussion our interest will center on the nature of the processes which lead to hyperossification. To start with, it is important to emphasize that estrogen treatment may produce extreme degrees of hyperossification in fully grown and sexually mature animals. This was found to be true for Pekin drakes. It is a fact that young cocks respond much more readily and much more extremely to estrogen treatment than do mature cocks. This may be considered an expression of age differences. It is true also, however, that mature Pekin and Mallard drakes, two varieties of the same species, do show even greater diversity with regard to the degree of hyperossification which is produced by excessive doses of estrogen.

It is obvious that age response-differences exist, a fact which has been previously demonstrated for mice by Silberberg and Silberberg.⁵ It is clear, too, that strains of the same species may vary widely with regard to the structural bone changes which occur, irrespective of age, after estrogen administration, and this also has previously been reported for mice (Gardner⁹). It appears, therefore, that the skeletal age *per se* and the presence or absence of cartilage in the long bones are not factors which directly regulate or influence the occurrence of hyperossification. Similar conclusions were reached by Sutro and Pomerantz²⁵ on the basis of observations on estrogen-treated dogs.

It can be seen that definite regularities exist with regard to the extent of estrogen-induced hyperossification if different parts of one and the same bone, or different long bones are compared with each other. In mice, Sutro¹⁴ observed that the lower part of the femur and the upper end of the tibia produced a greater amount of hyperossification than the rest of the appendicular skeleton. Zondek⁸ recorded for cockerels that the femur showed more extreme changes than the tibia and the latter much more than the humerus. Pfeiffer and Gardner²¹ found that in pigeons the femur exhibited greater alterations than the upper end of the tibia, the latter more than the remainder of the tibia, with still smaller responses for the radius and ulna. Our own findings are of a similar nature. In the leg bones of chickens and ducks the degree of hyperossification was greatest in the femur, less in the tibia and very slight in the tarsometatarsus. The lower end of the femur and the upper end of the tibia underwent more drastic changes than the other parts of these bones. As far as the wing bones are concerned, the situation is less consistent since the humerus, obviously on account of its pneumatic nature, showed little, if any, response to estrogen treatment.

It appears that the order in which the different bones and their parts respond is the product of interaction of a proximodistal gradient (di-

minishing blood supply) and of the order of growth intensity of different parts of the individual bones (probably again a question of blood supply). These sequences are not limited to estrogen treatment, but are found similarly in various pathologic conditions, *e.g.*, Albers-Schönberg (marble bone) disease, rickets, syphilitic osteochondritis (Schmidt ²⁶), scurvy and osteomyelitis (Harris ²⁷). The same sequence is evident when bone resorption occurs, as in experimental scurvy, after the administration of phosphorus and lead, and following treatment with parathyroid extract (Jaffe, Bodansky and Blair ²⁸). This cannot be mere coincidence, but must be an indication of the mechanism by which the phenomena of bone response are put into motion. Since we are dealing with the bones of adult animals, it is likely that the effects of growth intensity are indirect ones, *viz.*, a late consequence of events which occur during growth. An indication of the nature of these events can be seen in the fact that an opposite gradient exists in normal animals with regard to the percentage of ash and calcium in the long bones. In domestic fowls (and also in various mammals), ash and calcium content of the long bones has been found to increase proximodistally (Harshaw, Fritz and Titus,^{28a} Weakley and Dustman,²⁹ Landauer ³⁰). The more proximally a bone is located or the higher the growth intensity of one of its parts, the lower is its ultimate calcium content in normal development; and the lower the calcium content of an immature or adult bone, the more calcium will be deposited in response to estrogen treatment.

Our observations indicate that some relationship exists between the amount of endosteal trabeculae which are present in a particular bone and the degree of response elicited by estrogen treatment. This is borne out by comparisons of the behavior of the same bones in different varieties or species, of different bones within the same animal, or even of different parts of one and the same bone. The relationship is not a very close one, however, and the presence of trabecular bone cannot be considered a necessary antecedent to hyperossification. It is more likely that the variations in amount of endosteal bone and the varying degrees of estrogen-induced hyperossification trace back to another factor, common to both. This underlying pattern we believe to exist in the vascular supply to the bones. The observations of von Eggeling,³¹ Eckert-Möbius,³² and others have established the fact that a close parallelism exists between growth intensity of a bone, or of a particular part of a bone, and the degree of its vascularization; in fact, it had already been postulated by Kassowitz ³³ that the arrangement of the vascular pattern determines the growth architecture of bone. These persisting morphologic features of earlier growth differences

presumably are responsible, in growing and mature animals, for the specific patterns of bone resorption and of formation of new endosteal bone.

The foregoing interpretation is supported also by the sequence of phenomena as they occur subsequent to estrogen treatment. The first signs which could be discovered in our material always consisted of rarefaction (halisteresis) in the shaft and increased vascularization. The vascular changes, which presumably are responsible for the initial osteoporosis, can be seen in all parts of the bones: shaft, epiphyseal ends and marrow cavity. The haversian canals are widened and increased in number; there are more venules and arterioles. Subsequent vascular phenomena consist of stasis and formation of hematohyaloid. The early vascular changes in the shaft are followed by disappearance of fat from the marrow and by stimulation of marrow cell proliferation. The latter in turn leads to marrow fibrosis, to further vascular changes in the marrow, and finally to formation of endosteal bone.

Many steps in this sequence of alterations are by no means reactions which are exclusive features of bone. It is well known, of course, that estrogen treatment produces vascular effects in the mammalian uterus. Such changes, however, also occur very quickly in other parts of the body, *e.g.*, in the ear of rabbits or in the finger of humans where vasodilation can be observed within a few minutes after estrogen administration (Reynolds and Foster,³⁴ Reynolds³⁵). Formation of hyalin after large doses of estrogen and, secondarily, of epithelioid cells, were observed in the connective tissue of the uterine mucosa and muscularis of mice by Loeb, Suntzeff and Burns³⁶ and Suntzeff, Babcock and Loeb.³⁷ These authors stated that transudative changes are among the first found in the uterine wall (see also Arnold, Grumbrecht and Loeser³⁸) and that the hyaline substance may be produced by them. Again, it has been shown that in rats estrogen treatment leads to fibrosis in the uterine mucosa and submucosa (Burack, Wolfe and Wright³⁹).

These facts indicate clearly that the first skeletal changes, due to estrogen, are closely akin to those produced in other organs. It is only later that development proceeds as a typical local response, by formation of endosteal bone. It should be remembered in this connection that, to use Krompecher's⁴⁰ classification, it is only the "primary angiogenic" bone formation which in adult animals is affected by estrogen, and that, as is implied in the terminology, the blood vessels are of particular importance for this type of bone formation. In fact, primary angiogenic bone is the only kind for which it is definitely established that hyperemia leads to formation of new bone substance (Müller^{40a}).

It is well known that after fractures of long bones subperiosteal

bone formation occurs frequently at a considerable distance from the location of the fracture (Pollock and Ghormley⁴¹), and in the case of experimental fractures in canaries Roggemann⁴² has described all steps from initial resorption of fatty marrow to spongiosa formation throughout the whole length of the broken and healing bone. These changes also begin with a condition of hyperemia. Fibrosis and sclerosis of the bone marrow, as they occur in many pathologic conditions, can be traced back to hyperemia and blood stasis (Haslhofer⁴³). Among these, otosclerosis (otospongiosis) is of particular interest. For, it has been pointed out by Leriche and Policard⁴⁴ that this condition is the most characteristic result of vascular disturbance. It occurs most commonly, as the consequence of the calcium drainage during pregnancy, in women with great vasomotor sensibility of the face. It begins with resorption phenomena (rarefaction of bone) and ends in bone condensation (sclerosis).

Many details of the estrogen-induced bone changes bear a definite resemblance to the osteosclerotic phenomena which occur in certain blood diseases (pseudoleukemia, hemorrhagic aleukemia, polycythemia) and the sequence of changes appears to be much the same in the two instances (Schmidt,²⁶ Wolf,⁴⁵ Mettier and Rusk⁴⁶). There is reason to believe that in many, if not all, cases of this nature the bone changes are primary (Jordan and Scott^{46a}), and it may well be that the initial steps which lead to these osseous abnormalities are similar to those produced by estrogen.

It has been shown that hyperossification exists as a part of a seasonal rhythm in the females of certain species of birds. This is true of pigeons (Kyes and Potter,⁴⁷ Bloom, Bloom and McLean⁴⁸), English sparrows (Kirschbaum, Pfeiffer, van Heuverswyn and Gardner²²), quail (Ringeon⁴⁹), chickens (Bloom and Domm⁵⁰) and ducks (Bloom, Bloom, Domm and McLean,¹⁹ Benoit, Grangaud and Sarfati⁵¹). It may be assumed that the naturally occurring hyperossification and that produced by estrogen administration are both brought about by similar vascular stimuli. Estrogen appears to produce vasodilation in those parts which are either prominent heat-losing surfaces (ears, fingers) or which, for physiologic reasons, are especially responsive (uterus of mammals, marrow bones of birds). The rhythmic process of bony hyperossification in birds is an obvious adaptation to reproductive phenomena (shell formation) and as such occurs only in females. It appears from our observations, however, that the readiness of the bone circulation to respond to estrogen is present in males as well. Large doses of estrogen evidently produce vascular over-stimulation, leading to other pathologic processes (arteriolar hypertension, aneurysm).

All of our observations on endosteal bone formation, as a consequence of estrogen treatment, are, in our opinion, but a confirmation and extension of the statement by Leriche and Policard ⁴⁴ (page 32) that:

“Toutes les modifications dont nous venons de parler: oedème, multiplication des fibrilles, condensations préosseuses, paraissent dépendre des variations du régime circulatoire. Sans elles, ces modifications ne se produisent pas. Quand elles ont lieu, le régime circulatoire est toujours modifié. En définitive, la création d'un milieu ossifiable et la condensation préosseuse paraissent n'être que la conséquence des modifications circulatoires.”

Our observations fully agree with and give weight to Leriche's ⁵² (p. 310) generalization that:

“Il en résulte immédiatement ceci que, dans toutes les maladies avec ossifications, petites ou grandes, *l'ossification est, pathologiquement parlant, ce qu'il y a de moins important à étudier*. . . . Pour trouver le pourquoi des choses, il faut remonter à l'origine, chercher la cause et le mécanisme de la *raréfaction* qui a tout précédé, parce que c'est là que se trouve la raison immédiate de la néoformation osseuse. A l'origine de toute ossification, il y a un *processus de vaso-dilatation active*. . . .”

The early vascular changes can only lead to the formation of endosteal bone if the proper conditions are present within the marrow or bone cavities. Fibrous degeneration of marrow and hyalin furnish the substratum for calcification and ossification. In the absence of red marrow and blood vessels the processes leading to endosteal bone formation cannot occur. This situation presumably explains the differences in degree of response to estrogen treatment which exist between Mallard and Pekin drakes. The long bones (femur, tibia) of the latter are rich in red marrow and well vascularized, while those of Mallards have few white cells in their marrow cavities and a relatively poor blood supply. Similar conditions probably account for the differences in response between the tarsometatarsus and the other long bones of the leg.

It was found that some of the earliest skeletal symptoms of estrogen treatment (increased vascularization, stasis, formation of hyalin) can be produced likewise by injection of cholesterol (Fig. 21). No lipemia was observed in these cholesterol-treated animals (Zondek and Marx ⁵³). It is unlikely, therefore, that the lipemia which occurred as a consequence of estrogen injections was responsible for the circulatory changes which appear to mark the beginning of bone responses to estrogen.

The injection of oil (olive oil) alone produced a slight increase in vascularization of the bone marrow. All of the changes in bone which follow the injection of estradiol benzoate can, however, be called forth by the implantation of pellets of the hormone. Hence, it is clear that

the solvent (sesame oil) which was used in our experiments did not play a rôle in initiating the skeletal abnormalities.

Our material in no way suggests that estrogen has a specific stimulating effect on multiplication or activity of osteoblasts. On the contrary, all observations point to the conclusion that the eventual formation of large amounts of endosteal bone after estrogen treatment results chiefly, if not entirely, from metaplasia of the myeloid elements. This metaplasia may well be of the nature of a temporary cicatrization of the degenerating marrow.

It should be emphasized that the vascular stimulation in the bones of cholesterol-treated animals was not accompanied or followed by the appearance of new bone, whereas such bone formation did occur after estrogen injections. We are inclined to believe that these differences are of a quantitative nature, estrogen producing a more drastic vascular stimulation, but the existence of still other and more specific effects of estrogen is not excluded by the present evidence.

Finally, it should be pointed out that there was no obvious correlation between the size of the testes of the estrogen-treated animals and histologic structure of the bones. This holds for domestic fowls and both kinds of ducks. In fact, no consistent difference could be seen between cocks and capons in the kind and degree of effect which estrogen had on the long bones.

SUMMARY

Observations on long bones of cocks and drakes, which had been treated with estradiol benzoate, led to the following conclusions:

1. The earliest changes consist in an increased vascularization of the shaft of the long bones, accompanied by removal of bone salts (osteolysis).

2. The processes of halisteresis are followed by disappearance of fat from the marrow cavity, increased multiplication of marrow cells and vasodilation in the marrow.

3. After large doses of estrogen the marrow undergoes fibrous degeneration with focal necrosis, production of hyalin within and outside of blood vessels, and eventually the formation of new endosteal bone. Thickening of the walls of small vessels occurred at the same time.

4. There is a definite pattern of response of the various long bones. In the leg the femur shows the greatest changes, the tarsometatarsus the least. Similar patterns of response can be observed with regard to different regions of one and the same bone. These patterns correspond closely to the known differentials of growth activity and blood supply.

5. The skeletal changes after estrogen treatment are slight in Mal-

lard drakes and very pronounced in Pekin drakes, with cocks holding an intermediate position. Young cockerels show a much greater response than mature cocks. The effects are similar in mature cocks and fully grown capons.

6. It is believed that circulatory adjustments initiate the sequence of events which leads to final hyperossification, and that the formation of new endosteal bone represents a cicatrization of the degenerating marrow.

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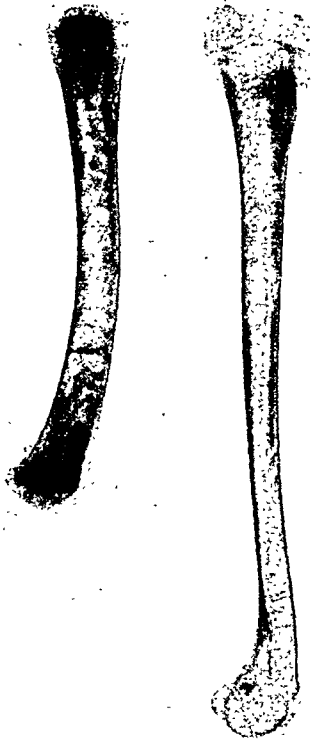
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DESCRIPTION OF PLATES

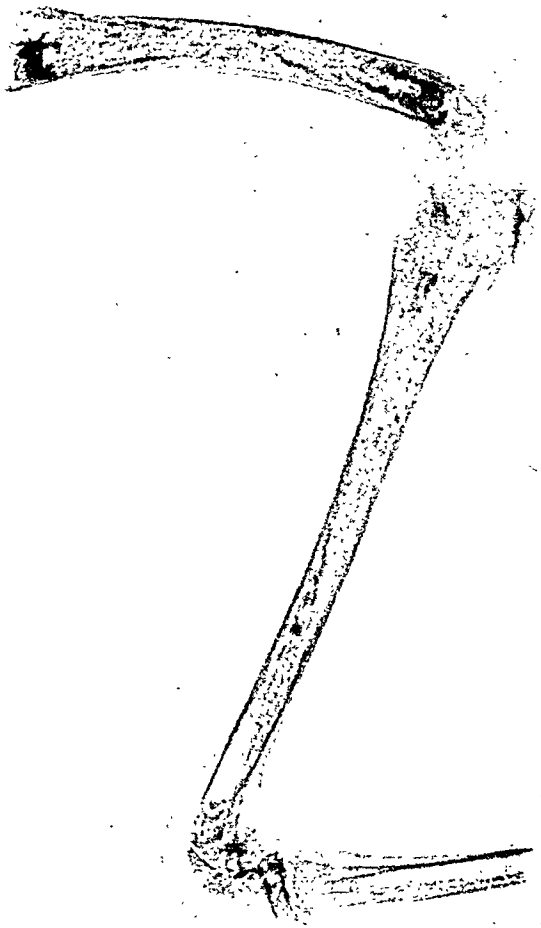
PLATE 32

- FIG. 1. Roentgenogram of femur and tibia of cockerel H75. Age, 11 weeks. Treatment: 5 mg. of estradiol benzoate twice weekly for 5 weeks. Bone density increased.
- FIG. 2. Roentgenogram of femur and tibia of cockerel H62. Age, 18 weeks. Treatment: 5 mg. of estradiol benzoate three times weekly for 12 weeks. Resorption of old and deposition of new bone.
- FIG. 3. Roentgenogram of femur, tibia and tarsometatarsus of cockerel H29. Age, 42 weeks. Treatment: 2.5 mg. of estradiol benzoate three times weekly for 36 weeks. Extreme bone condensation in femur and upper part of tibia; slight changes in lower end of tibia; normal tarsometatarsus.

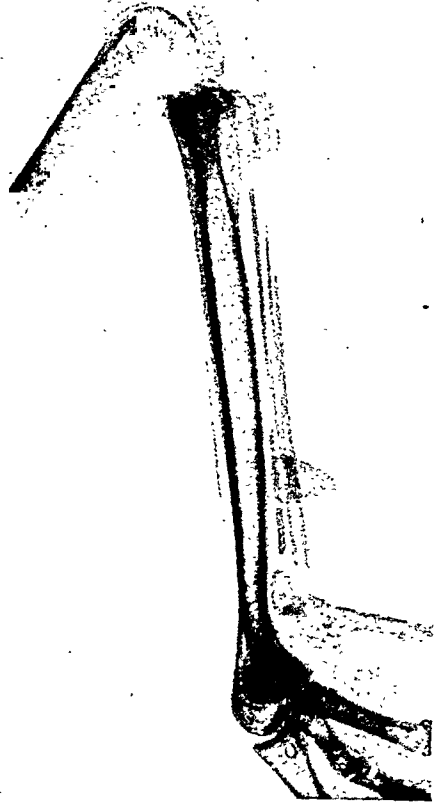
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3



Landauer and Zondek

Bone in Estrogen-Treated Birds

PLATE 33

FIG. 4. Roentgenograms of femora of adult Pekin drakes. From top to bottom, P_2 , P_1 , P_4 , P_5 , P_3 . The first and last bones (P_2 and P_3) are from untreated controls. The other bones are from animals which had been treated for 3 weeks with, respectively, 0.8 (P_1), 1.0 (P_4) and 2.0 (P_5) mg. of estradiol benzoate daily.

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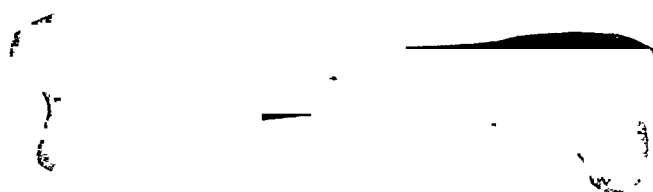
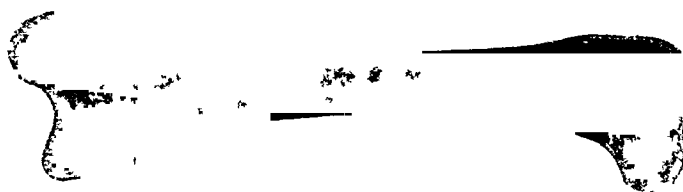
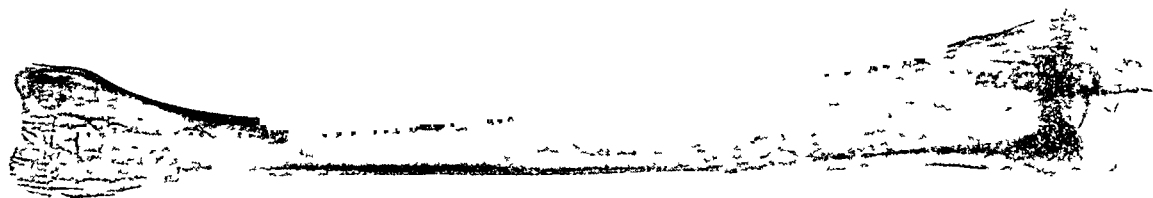
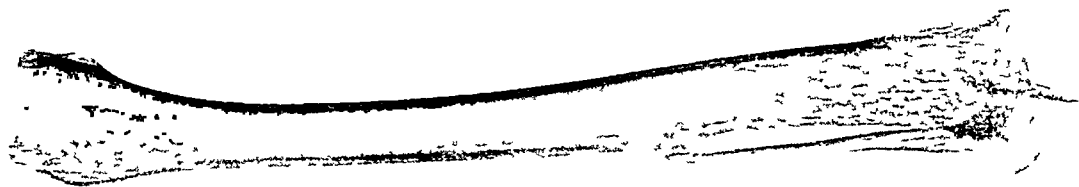
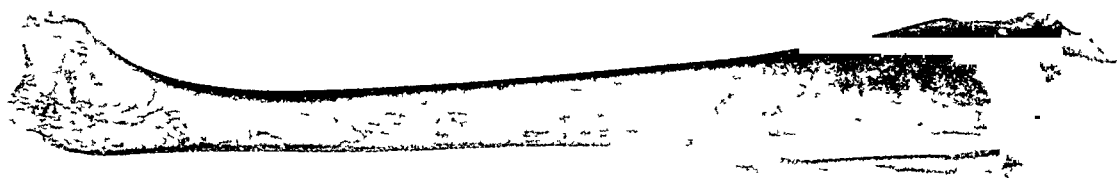
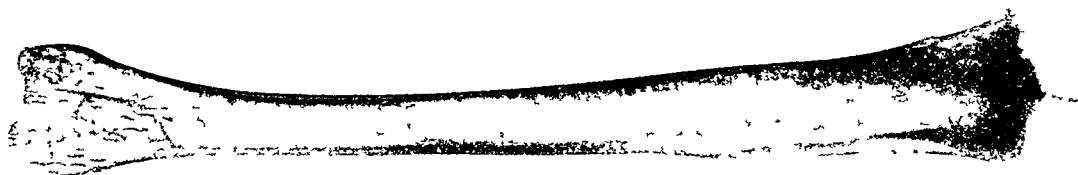


PLATE 34

FIG. 5. Roentgenograms of tibiae of the same Pekin drakes as shown in Figure 4. The changes in the tibia are less in degree than those in the femur. There is irregularity in bone deposition, and new bone is absent in the lower end of the tibia.



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PLATE 35

FIG. 6. Cock 5646, injected with 0.17 mg. of estradiol benzoate daily for 26 days. Frontal section of femoral metaphysis, showing halisteresis of old spongiosa. $\times 150$.

FIG. 7. Cock 4670, injected at first with 0.23 mg. of estradiol benzoate daily; dose later increased to 0.6 mg. Treated for 61 days. Total dose, 25.4 mg. Cross section of femoral diaphysis. To the right and below, shaft with osseous cavity containing new bone. To the left, newly formed bone in marrow cavity. Fibrous transformation of marrow. $\times 150$.

FIG. 8. Cock 5646. Frontal section of tarsometatarsal shaft. Fibrous degeneration of marrow in osseous cavities of periosteal bone. $\times 45$.

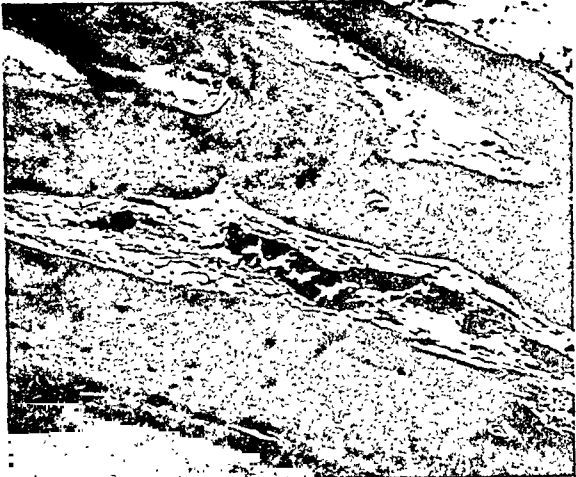
FIG. 9. Cockerel H29. Complete cross section of femoral shaft. Large numbers of new endosteal bone trabeculae are seen. Compare with Figure 15. $\times 6.5$.

FIG. 10. Cockerel H75. Cross section of tibial shaft. New endosteal bone. Three vessels with thickened walls. Large masses of pseudo-eosinophils which have undergone some degree of fibrous degeneration. $\times 45$.

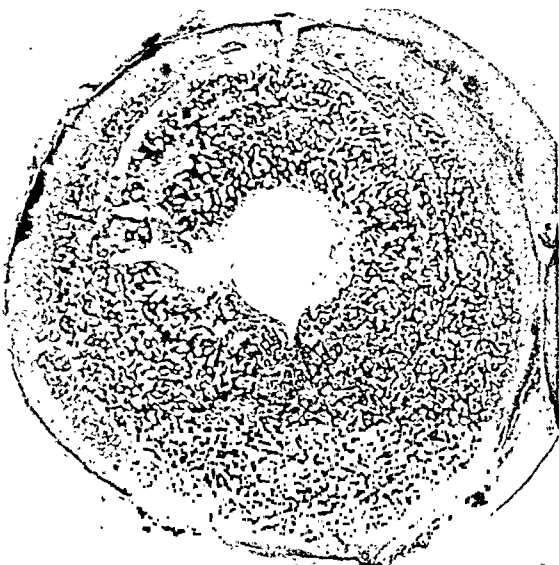
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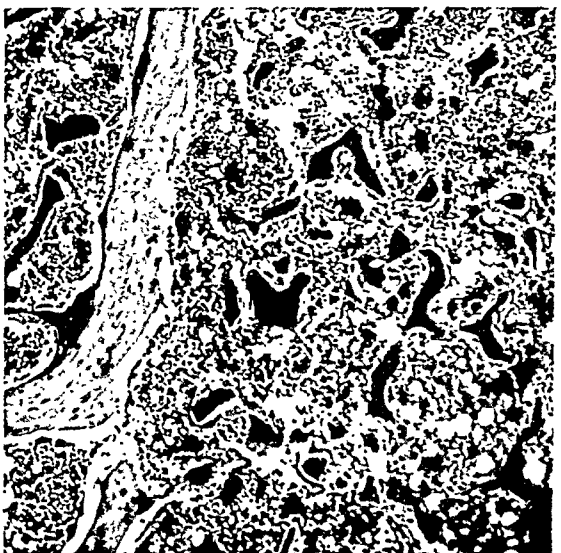
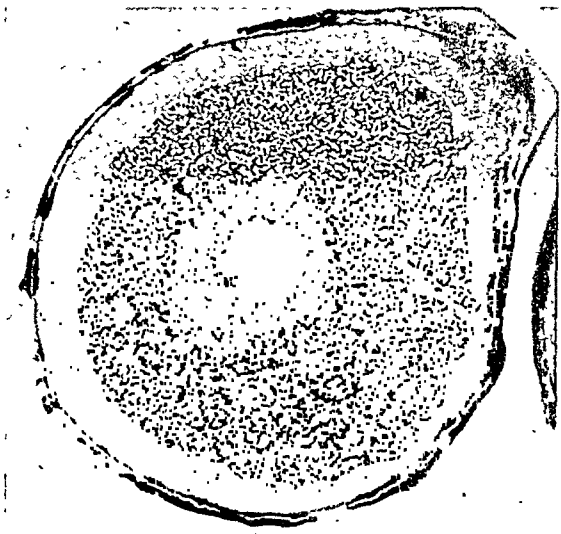
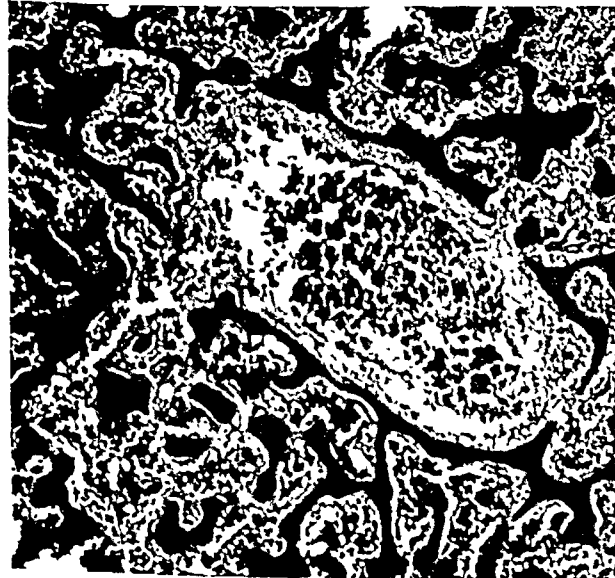
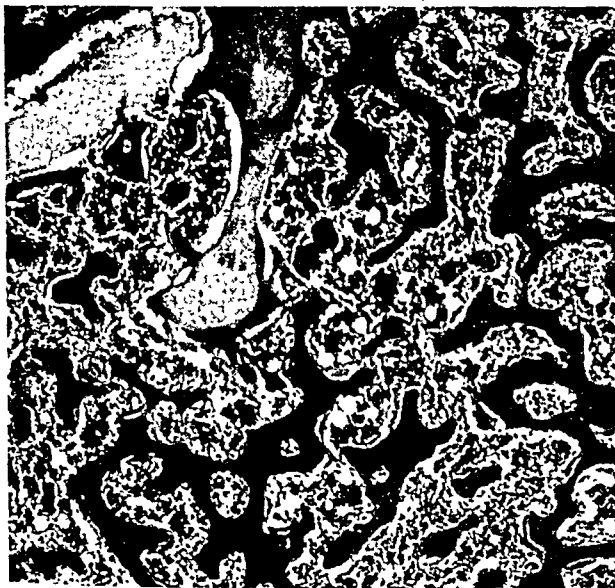
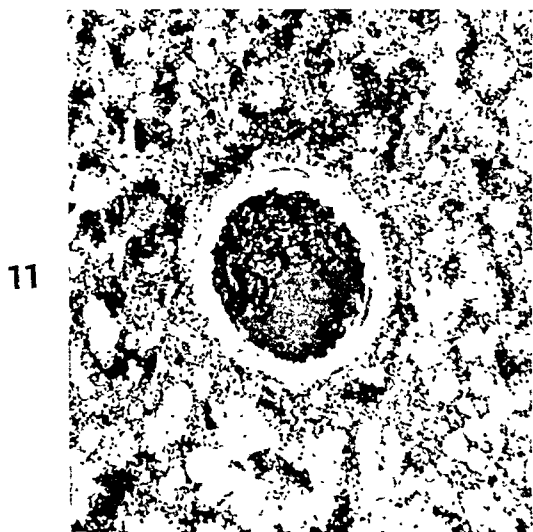


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PLATE 36

- FIG. 11. Cockerel H59, treated three times weekly for 3 weeks with 5 mg. of estradiol benzoate. Killed when 9 weeks old. Cross section of tibial diaphysis, showing a much enlarged venule filled with hyaline material. $\times 70$.
- FIG. 12. Frontal section through distal femoral metaphysis of Pekin drake P₄. Old (above and to left of center) and new endosteal bone. Hyperplastic marrow and extensive marrow fibrosis. Hyalin in upper left corner. $\times 45$.
- FIG. 13. Frontal section through proximal tibial metaphysis of Pekin drake P₅. Red cells and hyalin between trabeculae of new endosteal bone. $\times 155$.
- FIG. 14. Cross section of fibular side of tibial diaphysis of Pekin drake P₇. The inner surface of the large osseous cavity of the shaft, located here, is the only place where new bone was present. $\times 15$.
- FIG. 15. Complete cross section through the femoral diaphysis of Pekin drake P₅. Compare with Figure 9. Large amounts of new endosteal bone are present. $\times 6.5$.
- FIG. 16. Frontal section through the proximal tibial metaphysis of Pekin drake P₁. New bone trabeculae and osteoclasts. $\times 155$.



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PLATE 37

FIG. 17. Frontal section through the proximal tibial metaphysis of Pekin drake P₅. Cartilage in old endosteal bone, new bone spicules, complete fibrosis of marrow. $\times 55$.

FIG. 18. Frontal section through the proximal tibial metaphysis of Pekin drake P₄. Many new endosteal trabeculae, hyperplastic marrow, hyalin outside of vessels. $\times 45$.

FIG. 19. Frontal section through the proximal tibial metaphysis of Pekin drake P₄. Venule with hypertrophied wall and hyalin in lumen, surrounded by new bone. $\times 150$.

FIG. 20. Cross section of the humeral diaphysis of Pekin drake P₅. Much enlarged haversian canals in the shaft. $\times 150$.

FIG. 21. Cross section of the femoral shaft of cockerel H₇₄, treated with cholesterol (twice weekly 5 mg. of cholesterol in olive oil for $2\frac{1}{2}$ weeks, *i.e.*, a total of 25 mg.). Age, $8\frac{1}{2}$ weeks. Great increase in the number and widening of the haversian canals. $\times 45$.

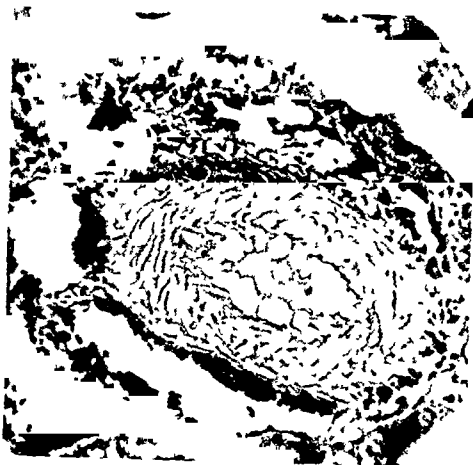
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EXPERIMENTAL STUDIES IN CARDIOVASCULAR PATHOLOGY

VIII. LATE VASCULAR REACTIONS OF HISTAMINE SHOCK IN DOGS *

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In a previous publication ¹ mention was made of the lesions noted in the organs and vessels of dogs which died within 48 hours after a histamine shock elicited by the subcutaneous injection of a suspension of this substance in a mixture of cotton seed oil and "Falba" absorption base.† It was noted then that an appreciable percentage of these dogs revealed marked edema and necrosis of the wall of the gallbladder, as well as hemorrhagic erosions and single or multiple ulcers in the prepyloric region of the stomach, with dilated and thrombosed vessels and arterioles with swollen and hyaline walls in the submucosa. There were also hemorrhages and leukocytic and mononuclear infiltrations with myocardial degeneration in the heart, associated with arterioles with swollen walls. In addition there was congestion and hemorrhage in the liver, and in the duodenal and jejunal mucosa, and hemorrhagic infarct-like areas in the spleen.

In subsequent experiments in which the same method of shocking was used, the organs of dogs which survived the shock and which were killed 8 days after this episode were studied. An opportunity was thereby provided to investigate the late effects in the various organs resulting from such circulatory and metabolic trauma. The present communication contains the results of this study.

EXPERIMENTAL PROCEDURE

A detailed histological investigation was made of the organs of 5 dogs weighing between 8 and 15 Kg. and belonging to a group of 100 dogs used to study the efficacy of methyl cellulose-S-methyl isothiurea solution in the treatment of histamine shock.² These particular dogs, among others, had survived the shock episode for 8 days. The shock had been elicited by the subcutaneous injection of histamine dihydrochloride (15 mg. per Kg. of body weight) suspended in a mixture of cotton seed oil (U.S.P.) and "Falba" absorption base (3 parts of oil to 1 part of absorption base). One cc. of the vehicle contained 20 mg. of histamine dihydrochloride. After such an injection the blood pressure dropped from a level of above 100 mm. Hg to 30 to 40 mm. within

* Received for publication, April 6, 1943.

† Falba is an oxycholesterin absorption ointment base, manufactured by Pfaltz and Bauer, Inc., New York, N.Y.

10 to 20 minutes and remained at approximately this level for several hours unless the treatment was instituted. Femoral blood pressure of dogs, which had been given nembutal, was recorded on a kymograph by means of a mercury manometer. The treatment, given 1 to 2 hours after the blood pressure had become stationary at the stated low level, consisted of intravenous infusions of a 0.075 per cent methyl cellulose (4000 centipoises) solution in normal saline to which S-methyl isothiurea (1:1000) had been added. Between 200 and 350 cc. of this agent, representing a combination of an aqueous solution of a highly viscous and hydrophilic colloid with a vasotonic substance, were given to the individual dogs. The blood pressure was restored thereby to, or near, the original level. After a preliminary observation period of 7 hours the dogs were removed from the operating table following ligation of the femoral artery, dusting of the wound with sulfathiazole and suturing of the skin. Eight days later they were sacrificed by the intravenous injection of 20 cc. of a 4 per cent formaldehyde solution. The autopsy was performed immediately afterward.

In general the gross examination revealed normal organs. One dog showed a stomach ulcer which was located about 1 inch above the pylorus and which measured approximately 1 cm. in diameter. The shallow floor of the ulcer consisted of a pale whitish tissue.

Histological Study

Brain. Minor small, round, cellular accumulations were present around the vessels in the region of the Ammon's horn in one dog. The vessels in the region of the basal ganglia of a second dog appeared as dark blue-stained tubes, while the meninges contained a mononuclear infiltration.

Hypophysis. The anterior lobe consisted mainly of eosinophilic cells, which, in one case, surrounded a small, basophilic, cellular accumulation. The posterior lobe was congested.

Lung. There were some scattered edematous areas present in the lungs of four dogs. The lung of the fifth dog was normal.

Heart. The myocardium, particularly the septum and papillary muscles, showed foci of mononuclear cells and fibroblastic proliferations, involving areas of granular muscular degeneration. Calcification of single muscle cells or groups of muscle cells was found in two dogs (Fig. 1). These degenerative changes were relatively extensive in one dog. The myocardial arterioles exhibited in one dog hyaline, polypous, intimal thickenings. In a second dog the arteriolar walls were occasionally swollen, hyaline and infiltrated by a few mononuclear cells.

Aorta. The middle and outer media of one aorta contained foci of

hyalinization and fibroblastic proliferation engulfing individual muscle bundles, while the vasa vasorum in the adventitia were surrounded by hyaline sheaths (Fig. 2). The middle section of the media in a second dog revealed a small focus of liquefaction necrosis which was surrounded by an increased number of muscle cell nuclei in radiating arrangement (Fig. 3). Small, bluish, calcified areas were present beneath the intima of the ascending and descending parts in a third dog, representing apparently calcified imbibition fluid in the subintimal space. A superficial diffuse calcification of a hyaline intimal thickening was found in one section, while in the second section a large fibrohyaline area existed in the middle and outer media (Fig. 4). The carotid artery contained also several subendothelial, granular calcium deposits. The middle media of the fourth dog revealed small foci of fibroblastic proliferation and a considerable edema of the inner media in the region of the arch. Beneath a diffuse intimal thickening, consisting of circularly arranged fibroblastic cells, small cavities were present bordering toward the outside on the internal elastic membrane (Fig. 5). The inner media was edematous, beneath a mucohyaline intimal thickening located 1 inch above the aortic valve (Fig. 6). Sections stained for elastic fibrils showed that the cavities were free from these elements and that the elastic fibrils in the adjacent parts of the aortic wall were rarefied and fragmented, while they were densely packed in some of the hyalinized areas of the media. The other large elastic arteries (carotid, femoral) were normal in all dogs with the exception of the one carotid artery mentioned.

Liver. There were numerous pericentral necroses present, associated either with congested capillaries or edema, or with fibroblastic proliferation containing numerous capillaries which gave to these foci an angioma-like appearance. The latter lesion was accompanied by an occasional hyaline thickening of the arteriolar walls. The Kupffer cells were swollen and loaded with a dirty greenish gray pigment. Similar cells were found within the fibroblastic pericentral foci.

Gallbladder, Pancreas, Intestine, Adrenal. Normal.

Stomach. The mucosa exhibited in one dog a defect which was filled by a proliferating fibroblastic mass which contained in its superficial parts hyalinized matter and leukocytes. The edematous submucosa showed dilated and hyperemic vessels. Some of the arteries in the submucosa had swollen hyaline walls. The stomachs of the other four dogs were normal.

Spleen. The pulp of one dog presented areas consisting of a fibroblastic thickened network, the meshes of which were empty. A coarse angiectatic structure was thus produced. The spleens of the other dogs

were normal except for some increase in brown-yellow hematogenous pigment.

Kidney. The tubular epithelium was vacuolated and frayed. There were scattered mononuclear foci in the interstitial tissue.

COMMENT

The late vascular and related organic lesions observed in dogs subjected to a fatal histamine shock illustrate again that a hypotensive mechanism can be just as effective in the production of vascular degenerative and sclerotic changes as a hypertensive mechanism.^{3, 4} These observations support the concept of Lange,⁵ who contended that arteriosclerosis is the result of a paresis of the innervated muscular media and a sequela of arteriohypotonia which causes a stagnation of tissue fluid in the vascular walls. They corroborate and extend those observations previously made by Heinlein,⁶ Meessen⁷ and Rühl,⁸ who found in rabbits chronically poisoned with histamine that the pulmonary arteries had a swollen and loosened media and local intimal thickenings, that the media of the coronary arteries was replaced by connective tissue and that the myocardium contained numerous necroses and hemorrhages. Meessen as well as Heinlein attributed these changes to the production of a stagnant anoxemia resulting from circulatory failure. The ensuing endothelial damage and increased vascular permeability to plasma ultimately leads to the development of sclerotic lesions.

While the dogs previously studied which died after a short interval of histamine poisoning exhibited the early lesions characteristic of circulatory disturbances (stasis; hyaline and erythrocytic thrombosis) and vascular hypotonic permeability (swelling, edema and hyalinization of walls), those of the present investigation reveal definite late effects of such episodes upon the vascular wall. The bluish-stained incrustations of the cerebral vessels of one dog are anatomically and topographically similar to those found as the result of anoxemic episodes elicited by carbon monoxide and lead poisoning. Morphologically they carry a close resemblance to the pseudocalcifications of the cerebral vessels described by Ostertag,⁹ who related their massive appearance to endocrinic disturbances of the calcium metabolism.

Although the occurrence of calcification of the subintimal plasmatic fluid and of the muscle cells of the heart, present in several dogs, might support this view, such changes may occur also in the absence of demonstrable disorders of calcium metabolism when necrosis occurs in the myocardium and vascular walls (adrenalin necroses). The repeated observation of small cavities in the aortic media, representing the re-

sults of liquefaction necrosis preceded apparently by a local loss of nuclei and homogenization of the media and followed by the formation of a fibroblastic scar, has a certain similarity to the medionecrosis aortae idiopathica cystica described by Erdheim.¹⁰

The therapeutic agents administered in an attempt to control an otherwise fatal shock have no part in the production of the described vascular and organic changes, as the intravenous injection of methyl cellulose solution in amounts far exceeding those given to the dogs in this experiment elicits lesions which differ fundamentally from those reported here.

CONCLUSIONS

Dogs surviving a severe, prolonged and usually fatal histamine shock developed degenerative, cystic and calcifying lesions in the aorta, particularly of its media, as well as in the smaller arteries (carotid, coronary, cerebral, gastric). The heart showed myocardial degenerations, with calcification and mononuclear and fibroblastic foci.

The most striking late results of the transitory circulatory and vascular reactions of histamine shock were: prepyloric peptic ulcers, pericentral hepatic necroses with hemorrhages and fibroses, and focal splenic fibroblastic proliferations.

The observations provide additional experimental evidence for the claim that hypotensive agents may elicit sclerotic arterial lesions.

The late vascular, cardiac and parenchymatous organic lesions observed after acute but prolonged histamine shock may thus not only provide the anatomical basis for delayed deaths after shock, but also for cardiovascular changes attributed in general to arteriosclerosis.

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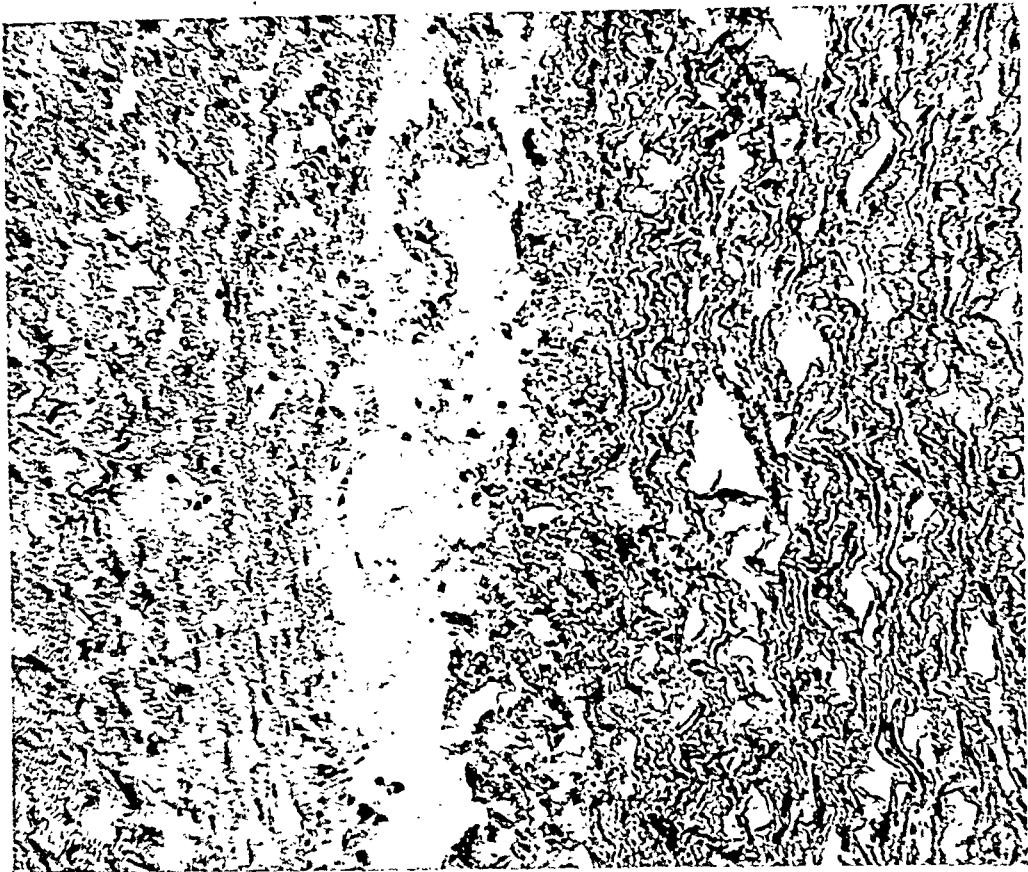
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PLATE 39

FIG. 3. Cystic cavity with ragged edges containing a faintly stained and scanty albuminous material located in middle third of media of the aorta. Hematoxylin and eosin stain. $\times 120$.

FIG. 4. Large area of mucinous hydropic degeneration surrounding vasa vasorum with thickened walls in the aortic media. Hematoxylin and eosin stain. $\times 120$.

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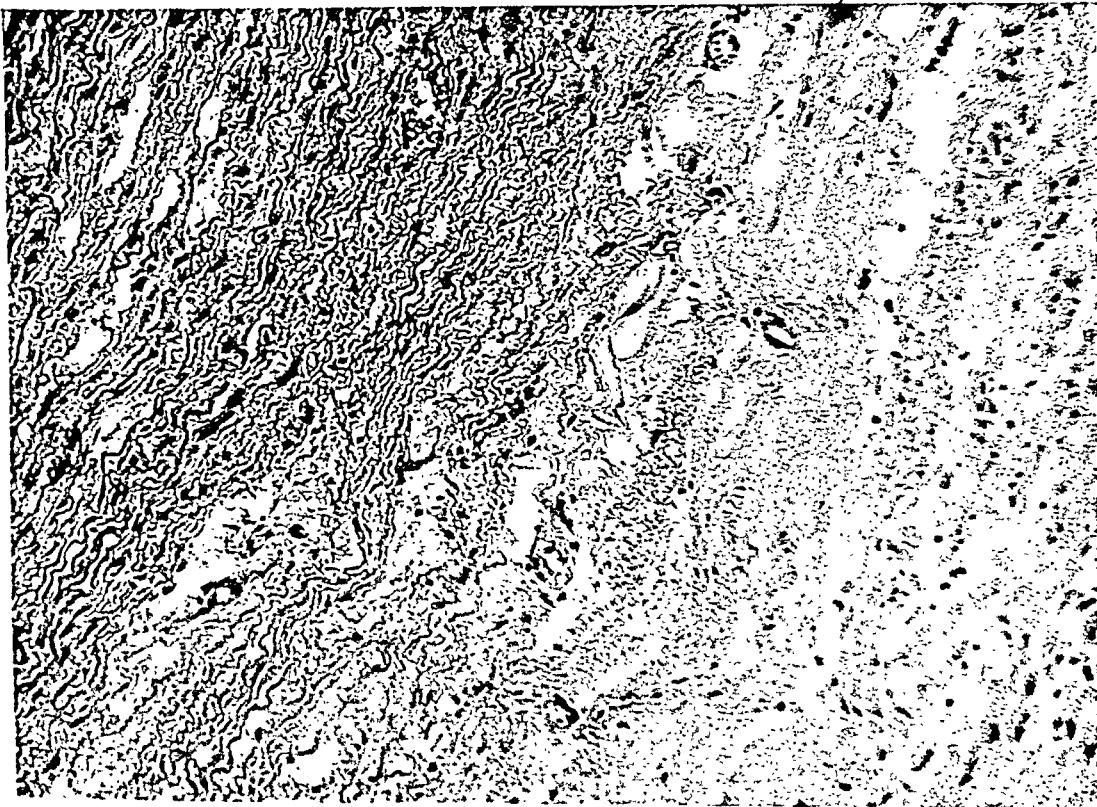


PLATE 40

FIG. 5. Two large cystic cavities with degenerative changes in the adjacent tissue are situated in the middle media of the aorta. A large area of homogenization is located in the outer third of the media. Hematoxylin and eosin stain. $\times 120$.

FIG. 6. Much thickened aortic intima with small cystic cavity filled with a mucinoid material located adjacent to internal elastic membrane. Hematoxylin and eosin stain. $\times 150$.



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CONCRETIONS IN THE ANTERIOR PITUITARY LOBE OF THE HUMAN EMBRYO AND THE NEWBORN *

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While examining pituitary glands of newborn children, the senior author, years ago, was struck by the finding of colloid † concretions in the anterior lobe. A search of the literature concerning them yielded little information. Erdheim mentioned the finding of a few calcific concretions in the anterior lobe of a man, 56 years old, who died of carcinoma of the esophagus. He distinguished them from the meningeal concretions as found on the capsule of the pituitary gland.

Lucien and Parisot saw small, round, calcific concretions in the anterior lobe in one case; they did not state age or sex.

Kraus, in a paper on the lipid substances in the hypophysis, casually mentioned that he had seen, repeatedly, concentric laminated calcific concretions in the anterior lobes of embryos and young infants. In later writings, Kraus referred to the same finding as obviously non-pathologic.

Most of the numerous textbooks and monographs that were consulted do not refer to the subject. The occasional mention of concretions, *i.e.*, von Gierke in Aschoff's textbook, 1936, leaves one in doubt whether the colloid concretions within the anterior lobe are referred to or the calcific bodies in the meningeal investment of the organ. Rasmussen's paper deals only with the latter. An extensive, but necessarily incomplete, survey of pertinent embryologic, experimental and endocrinologic literature was fruitless.

This paper will not deal with pituitary concretions as found in various diseases (for instance, Simmonds' disease, adiposogenital dystrophy, hemorrhage in anterior lobe, tumors of anterior lobe). We are concerned only with concretions originating in the normal anterior lobe and the pars intermedia, especially in the fetus and the newborn.

* Received for publication, May 1, 1943.

† Throughout this paper the word "colloid" is used in a general sense, without commitment as to chemical nature, and in default of any other fully acceptable term.

CONTROLS

Failure to observe concretions in a fairly extensive experience with the adult human pituitary gland could not be accepted as a satisfactory negative control. Therefore, 110 pituitary glands from persons more than 1½ years of age (most of them between 40 and 70 years) were subjected to special search. Of these, 6 showed numerous concretions comparable to the ones in the newborn pituitary body; the ages were 3, 46, 52, 56, 65 and 68 years. In 8 instances, only one, or very few, concretions were found. In this group the ages were 8, 13, 45, 51, 53, 57, 60 and 62 years. In each of these 8 cases 50 sections were carefully searched. In 6 of the negative controls, more than 60 sections were examined; in 11, more than 50; in 20, more than 40. In 8 of the negative controls, sections were systematically studied under high magnification. Neither age distribution nor sex distribution of the positive controls was significant. No disease or group of diseases was prevalent among the positive controls. In 5 instances, with only few sections available, no decision could be reached as to the presence or absence of concretions.

MATERIAL AND METHODS

The pituitary glands of 150 newborn children and young infants were examined. The organs were fixed in formaldehyde, embedded in paraffin and the sections stained with hematoxylin and eosin. Some were studied serially. On the average, about ten sections of every pituitary gland were available. In all newborn infants, including several anencephali, concretions were present. They were found also in most of the infants who had died before the sixth postnatal month. The youngest age at which concretions were absent was 2 months (male, 58 cm. long; female, 50 cm. long). In one male, 48 cm. long, who had lived for 2 months and 7 days, very many concretions were present. Of the three 3-months-old infants the first had very few concretions; the second, none; the third revealed only one doubtful concretion in a series of 192 sections. There was only one specimen from the fourth postnatal month; it contained concretions in very small numbers. There were three from the fifth month: one positive, the second with very few, the third one negative. But all of the four pituitary glands of the sixth postnatal month did contain concretions, one in moderate numbers, one few, two very few. The 7½-months-old infant had few, one from the eighth month none. In the 19 sections of the anterior lobe of a boy, 1½ years old, none could be found; but there were occasional concretions in the pituitary gland of a boy, 2 years and 2 months old, with 49 sections available. Thus, in spite of the small

number of cases, the conclusion seems warranted that the concretions tend to decrease or disappear in early infancy. In the pituitary gland of the embryo and the newborn the concretions were found easily; in all other age groups one had to search for them patiently. There was no difference in the occurrence of concretions between males and females.

In most specimens a magnification of $75\times$ was sufficient. Some slides were studied at $160\times$ magnification and in selected cases we made sure of the absence of even the smallest concretions by searching many fields under still higher magnification ($280\times$).*

Fourteen embryonic pituitary glands were studied; they all contained concretions, mostly in large or moderate numbers. The two smallest embryos measured 55 mm. crown-rump length; in one, few were found; in the other very many, up to 30 in one section.

LOCATION OF CONCRETIONS

Practically all of the concretions in the infants and the older fetuses were situated in the anterior lobe proper. Only an exceptional one was seen in the pars intermedia or the pars tuberalis. The smallness of these areas may be a sufficient explanation. The distribution of concretions in the anterior lobe in relation to periphery and center, neighborhood of the cleft or the stalk, did not seem to follow any rule. The majority of the concretions were surrounded by epithelial cells in irregular fashion, without prevalence of one of the three cell types. About one concretion out of ten appeared to be surrounded by epithelial cells with a more or less radial arrangement. This, in accordance with the histologic picture, was more frequent in younger embryos. The lumen, in which such concretions seemed to be situated, might be a shrinking space. The anterior lobe contains so many capillaries that, by necessity, some concretions must be situated near them. Occasionally the picture was that of a concretion in the lumen of a capillary (Fig. 13). Colloid in a sinusoid of the anterior pituitary lobe is not unusual; thus, a colloid concretion might be intracapillary as well. But it is possible also that the concretion has torn the delicate capillary wall while the paraffin block was being cut.

DESCRIPTION OF CONCRETIONS

More than half of the concretions were ovoid, about one-fifth were irregular in shape, some were round, and a few pyramidal. The average size was 18 by 13 μ , the largest one was 80 μ long; there were many

* Since these investigations were concluded, many more pituitary glands of newborn children and of adults have been examined. Concretions were found regularly in the newborn.

small ones down to $4\ \mu$ in diameter. There was no significant variation in size with age and sex. However, in a few younger embryos, large concretions were conspicuous in the anterior lobe and in the pars intermedia. The concretions assumed a great variety of hues in the hematoxylin and eosin stain. Most of them stained purplish blue, some were a pure blue, others pinkish blue; only a few were pink or red. Some, which appeared to be very hard structures, did not become deep blue with the hematoxylin and eosin stain, as calcific masses are supposed to do. The hardness of the concretions was attested to by their breaking and by the frequent tearing of surrounding tissues.

In a human embryo of 55 mm. crown-rump length,* many, partly very large, concretions were found. Some of them, reaching a length of $80\ \mu$, were visible with a hand lens. They were club-shaped, sausage-shaped or irregularly pyramidal. One, which was $70\ \mu$ long, had several gentle indentations. Since the average thickness of the large concretions was 10 to $12\ \mu$, some of the small concretions might represent cross sections of large ones. There were, however, numerous very small particles with the same optical characteristics. They were mostly situated in spaces which were surrounded by epithelial cells while the large concretions were found in solid epithelial masses. At the lower surface of the pituitary gland a group of concretions seemed to lie outside the epithelial organ in a kind of "bay" as if the surrounding epithelial cells had retracted from it (Fig. 1). Probably these relatively large, firm masses had led to pressure atrophy of the epithelial cells by which they were formed. Figure 5 from the pars intermedia of an embryo, 9 cm. long, may represent an earlier phase of this process. Only with reluctance can one accept such pictures as denoting a "normal" developmental process.

About half of the concretions were more or less laminated (Figs. 9, 10, 12, 13, 14 and 20). In embryos up to 29 cm. crown-heel length, lamination was seldom distinct. On the whole, indistinct lamination was three times as frequent as distinct lamination. The concretions, laminated or not, revealed their character as solid bodies by their irregular shape and by festooned or jagged edges. Colloid masses, which before fixation were fluid or semifluid, have a smooth, regularly convex contour. The presence, size and shape of shrinking spaces next to the concretions could not be used as an indicator of their consistency.

LARGE CALCIFIC CONCRETIONS

In five cases the anterior lobe contained larger calcific masses which were different from the colloid concretions (female, 57 years, pheno-

* Columbia Study Collection, no. 2034, courtesy of Dr. Tracy J. Putnam.

barbital poisoning; male, 60 years, carcinoma of bladder; male, 40 years, septic endocarditis; male, 50 years, diabetes; female, 37 years, rheumatic heart disease). These concretions were situated in the most dorsal portion of the anterior lobe, an area which often is rather fibrosed in older persons. They reached one-tenth, in one of the cases almost one-third, of a millimeter in diameter (Figs. 7 and 8). They essentially represented thin concentric shells. But there also were compact calcific masses; they stained inky blue with hematoxylin; they did not take any eosin. Some of the thin fragments remained unstained and appeared highly refractive and light brown.* These concretions bear a certain resemblance to those which Wislocki found in the anterior lobe of a 30-year-old elephant. The concretions in the pituitary gland of the elephant definitely were connected with the colloid. Since these larger concretions in the human adult are situated in a region of the anterior lobe which normally is rich in connective tissue, one cannot assume scarring in their neighborhood. But in two of these five cases, indistinct giant cells were found near the calcific masses, indicating foreign body action. As previously mentioned, we have never seen any tissue reaction around the ordinary colloid concretions in the newborn. Possibly these large concretions do represent calcification of large colloid masses which are surrounded by connective tissue directly, the epithelium having disappeared. Inside the calcific ring in Figure 8 the colloid is still recognizable and atrophic epithelium is seen in the neighborhood.

The lancet-shaped calcific mass within colloid, shown in Figure 19, represents an isolated observation.

CONCRETIONS IN ERDHEIM GLANDS

In one instance only were concretions found in Erdheim glands (Figs. 15 and 17). They are different from the other concretions in their aspect and, more important, in their partly intracellular location. One might assume that the cell formed its product but did not expel it. Little seems to be known about the secretory mechanism of the Erdheim glands (Rasmussen). Figure 16 definitely shows secretion granules in the epithelial cells of an Erdheim gland.

CONCRETIONS IN OTHER FETAL ORGANS

The question arises whether or not concretions are found during fetal life in organs other than the pituitary body. No systematic search in

* Obviously Erdheim has seen such concretions in a 20-year-old patient who died of heart disease. Erdheim described them as concentrically laminated lime capsules which formed large agglomerations.

this direction has ever been undertaken as far as we know. But a few observations are available. In the otherwise normal kidney cortex of a full-term male infant, 5 hours old, a laminated concretion was found. It was surrounded by normal tubular epithelium. The pyramids in this kidney did not contain concretions.

In the fat tissue outside the suprarenal gland of a male fetus, 20 cm. long, small, ovoid, structureless, calcific masses were situated.

Hassall's corpuscles sometimes calcify during fetal life, completely or partially. This change has been observed by Hammar and we have repeatedly seen it.

In the epithelial lamella which connects glans and prepuce during fetal life, horny pearl-like bodies are regularly present. Stieve mentioned their calcification in the newborn. We have seen a partly calcified one in a fetus of 22 cm. crown-heel length. Identical structures can be found in the corresponding lamella of the preputium clitoridis.

We have never seen concretions in the thyroid of the fetus or the newborn. In these stages the thyroid follicles contain little or no colloid. But even in the adult thyroid concretions are very seldom encountered.

The cysts, which in the adult so frequently are found between the anterior and posterior lobes of the pituitary gland, often are distended with dense colloid matter but they never contain concretions. Thus, inspissation alone does not explain the forming of the concretions. If, as we may assume, colloid masses in the pituitary gland are similar to those found in the thyroid, their water content is very low, giving small leeway for inspissation.

COMMENT

Since the concretions are found in the pituitary gland of the fetus and the newborn in practically 100 per cent of the specimens examined, we have to consider these findings statistically normal. The question whether they also conform with an idealistic norm may appear gratuitous; it may seem a relic from times when man believed in the infallibility of creative nature. But the question may help us in a certain way. These concretions are found in the embryo and in the newborn; they tend to disappear in early postnatal life. Hence it seems logical to assume that some maternal influence is responsible for their formation and maintenance. The findings thus can be considered together with other phenomena which are caused by hormonal, or other, maternal influence. Such findings are: colostrum secretion in the newborn, hyperemia and hemorrhage in the endometrium of the newborn, maturing of ovarian follicles in the embryo, enlargement of the uterus, hypersecretion of cervical glands, squamous metaplasia in the prostate.

In 1914, Alfred Kohn, the anatomist in Prague, in a very interesting paper, discussed these and similar findings. He designated the whole complex of these findings in the newborn as a "miniature puberty." * He mentioned that even acne, such a typical phenomenon of puberty, occurs in the fetus and in the newborn. He also pointed out, in this connection, the hypertrophy of the suprarenal gland with the postnatal degenerative processes, and the enormous masses of interstitial cells in the ovary and testicle of the equine fetus. These interstitial cells decrease toward the end of intrauterine life and disappear in the first postnatal month. In the testicle of the human fetus, also, interstitial cells are very numerous. As Kohn puts it, we are dealing here with transitory phases of irritation caused by substances coming from the maternal organism.

The placental circulation exposes the embryo to influences which are not entirely adequate, since substances for which the embryo may have no use are carried to its organs, *e.g.*, the sex hormones, even of the opposite sex. The changes caused by the hormones do not, according to present-day knowledge, damage the embryo. Pressure atrophy of epithelium, however, as caused by the pituitary concretions (Fig. 5), borders on the pathologic.

The distention of hair follicles and of sebaceous gland ducts, as found to a high degree in acne of the newborn, and to a lesser degree in almost every newborn, represents a picture which would be called seborrhea or comedo in the adult. That means it would be considered as a disease.

Finally, erythroblastosis fetalis is a fatal disease in which incompatibility between maternal and fetal blood plays a rôle. Such a disease could hardly be imagined in an oviparous species. To date our knowledge of fetal and neonatal disease is fragmentary. It remains to be seen what rôle similar incompatibilities between mother and fetus play in unexplained death of the fetus, especially in habitual abortion.

SUMMARY

1. Colloid concretions are a constant finding in the anterior pituitary lobe and in the pars intermedia of the human fetus and the newborn.
2. Most of the concretions disappear in the first postnatal months.
3. Large calcific bodies are sometimes found in the anterior pituitary lobe of the adult.
4. We believe that the concretions in the fetus are formed under the influence of maternal hormones, thus adding to the group of conditions

* This expression was first used by Jacquet and Rondeau in 1905. These authors, however, did not believe that the phenomena in question were caused by the hormones of the mother.

in which there are biologic and possible pathologic implications of maternal hormone action upon the fetus.

5. In one instance, concretions which were partly intracellular were found in Erdheim glands.

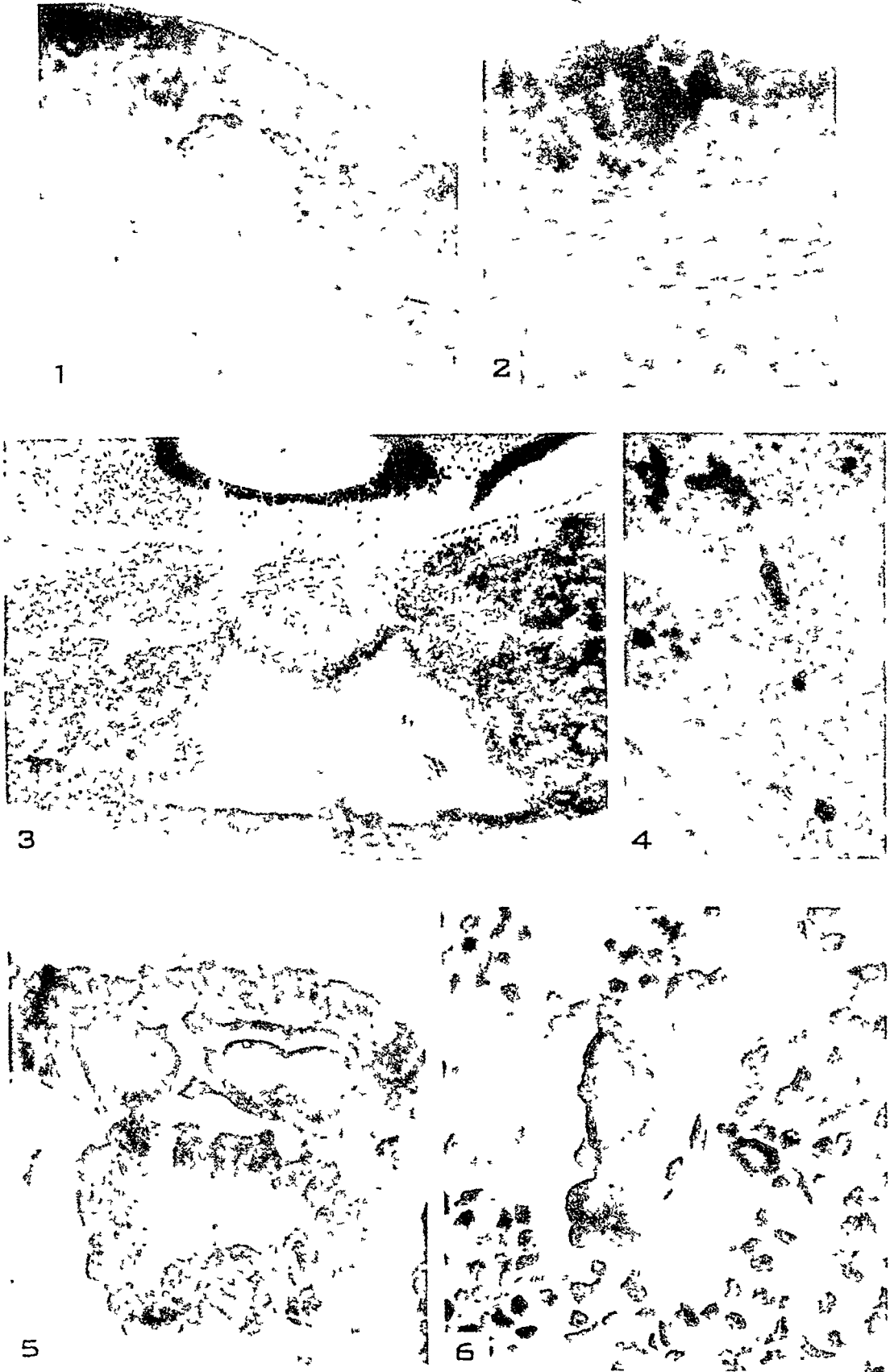
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DESCRIPTION OF PLATES

PLATE 41

- FIG. 1. Embryo no. 2034, Columbia Study Collection, 55 mm. crown-rump length. Concretions next to thinned-out epithelial lining of pituitary cavity. $\times 360$.
- FIG. 2. Same specimen as shown in Figure 1. Large, irregularly shaped concretion in lining of pituitary cavity. $\times 360$.
- FIG. 3. Same specimen as shown in Figures 1 and 2. General view of pituitary region. Sphenoid cartilage at bottom of photomicrograph; brain ventricle at top. A large concretion is present in the left lower corner. $\times 80$.
- FIG. 4. Same specimen as shown in Figures 1 to 3. Sphenoid cartilage just visible in left lower corner. Anterior lobe tissue with many concretions, four of which are in focus. $\times 360$.
- FIG. 5. Path. no. 35948, 9 cm. crown-rump length. Sex unknown. Epithelial lining of pituitary cavity thinned out by concretions. $\times 750$.
- FIG. 6. A-44-40, female newborn, lived for 32 hours. Anatomic diagnosis: multiple hemorrhages. Large, irregularly shaped colloid concretion in anterior lobe, a smaller one next to it. $\times 670$.

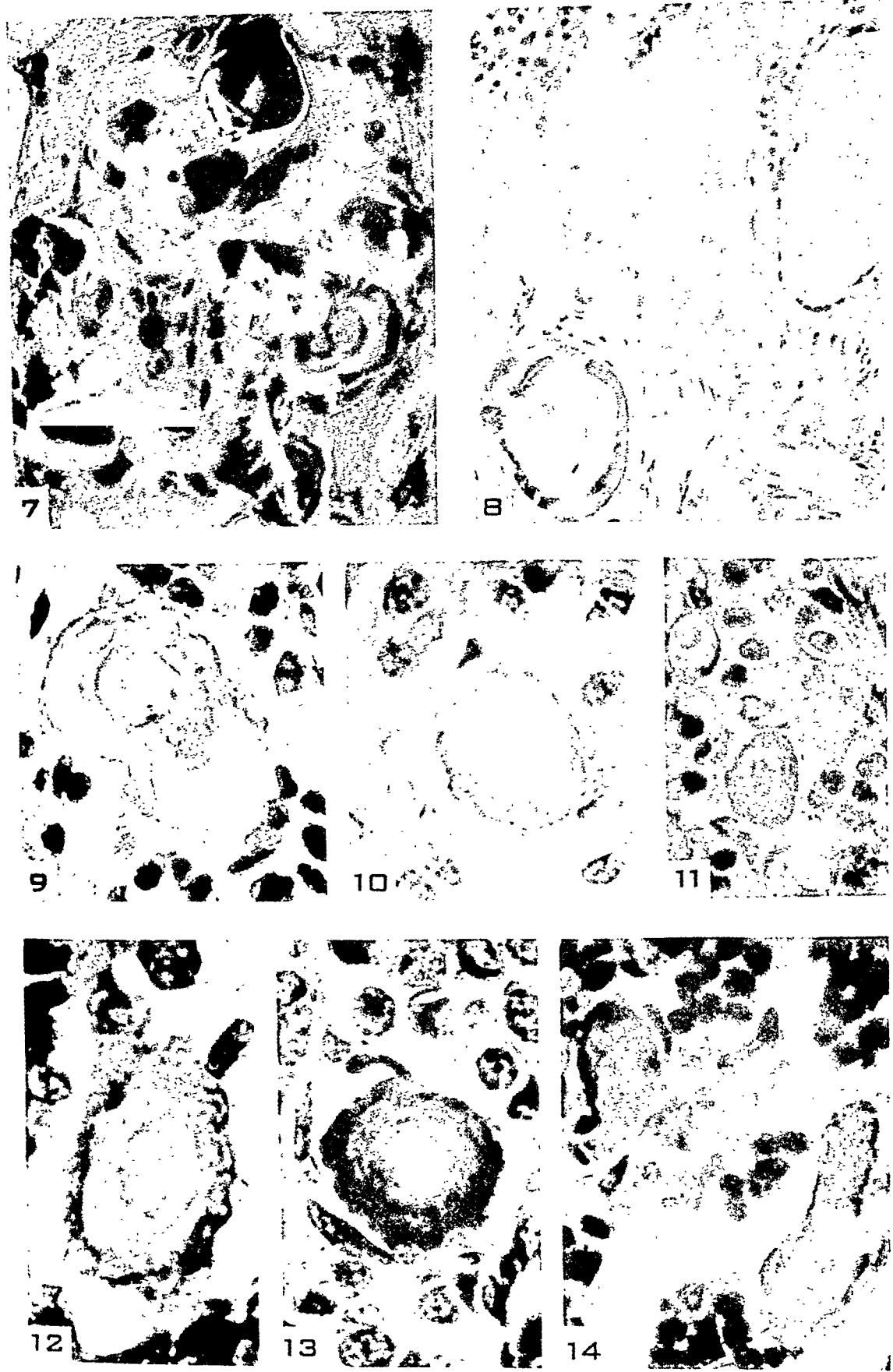


Plaut and Galenson

Concretions in the Anterior Pituitary Lobe

PLATE 42

- FIG. 7. Adult. No clinical data available. Large, broken, calcific masses in anterior lobe. $\times 600$.
- FIG. 8. A-49-41, female, 57 years old, who died of phenobarbital poisoning. Calcific ring at periphery of colloid mass. An ordinary colloid mass, still surrounded by flattened epithelial cells, is seen in the right upper corner of the photomicrograph. The field is taken from the somewhat fibrosed posterior portion of the anterior lobe. $\times 220$.
- FIG. 9. A-70-33. Male anencephalus, 1 day old. Concretion with much variation in density of different layers. No shrinkage space around concretion. $\times 700$.
- FIG. 10. A-111-38, female, 19 days old. Multiple malformations; mongolism. Small colloid concretion with beaded edge and laminated margin. The center appears homogeneous. $\times 700$.
- FIG. 11. A-53-38, female, 1 day old. Intracranial hemorrhage. Typical colloid concretion. Lamination is visible. The edge is partly beaded. The surrounding tissue appears unaltered. $\times 750$.
- FIG. 12. A-107-37, male, 10 hours old. Doubtful pneumonia. Dense beaded edge. Distinct lamination. $\times 900$.
- FIG. 13. A-186-35, female, 21 days old. Cerebellar hypoplasia with meningocele. Compact concretion, perhaps intracapillary, with three spindle-shaped nuclei surrounding it. $\times 900$.
- FIG. 14. A-48-37, male stillborn, 43 cm. crown-heel length. Multiple hemorrhages. Colloid masses with faint traces of lamination. The capillaries are very wide, as frequently found in the newborn. $\times 900$.

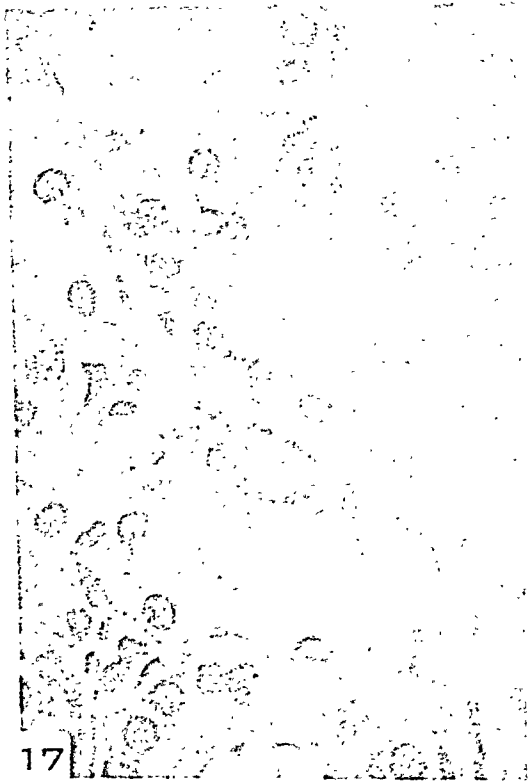
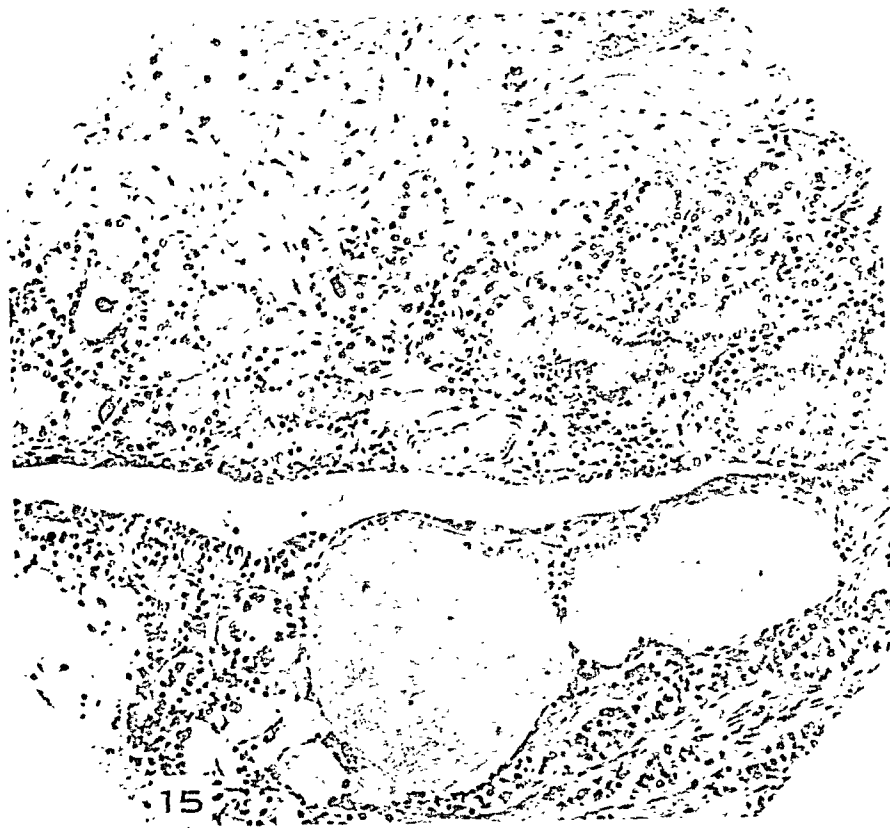


Plaut and Galenson

Concretions in the Anterior Pituitary Lobe

PLATE 43

- FIG. 15. A-36-34, male 13 years old. Tuberculous meningitis. The hypophyseal cleft runs horizontally through the photomicrograph, separating the anterior lobe (below) from the posterior lobe (above). Erdheim glands occupy an unusually large area next to the cleft. They contain three concretions (left half of picture). The two upper ones are luminal, the lower one is intracellular. $\times 150$.
- FIG. 16. A-176-35, female stillborn, 50 cm. crown-heel length. Secretion granules in Erdheim gland. Nuclei at base. $\times 1500$.
- FIG. 17. The left lower concretion from Figure 15, at higher magnification. The concretion is situated within an epithelial cell. The narrow round lumen of the Erdheim gland is seen below the concretion. $\times 670$.

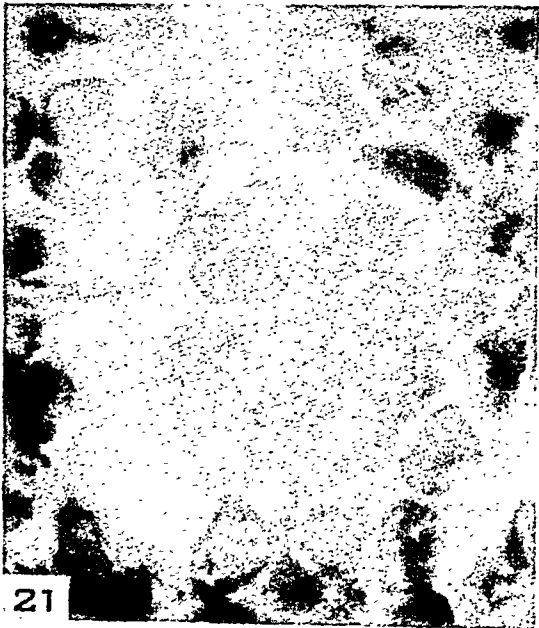
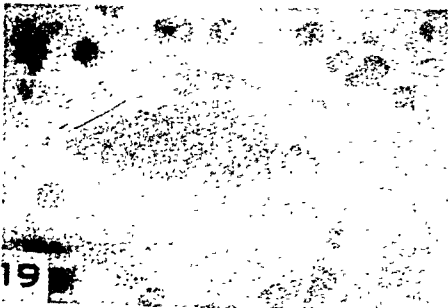
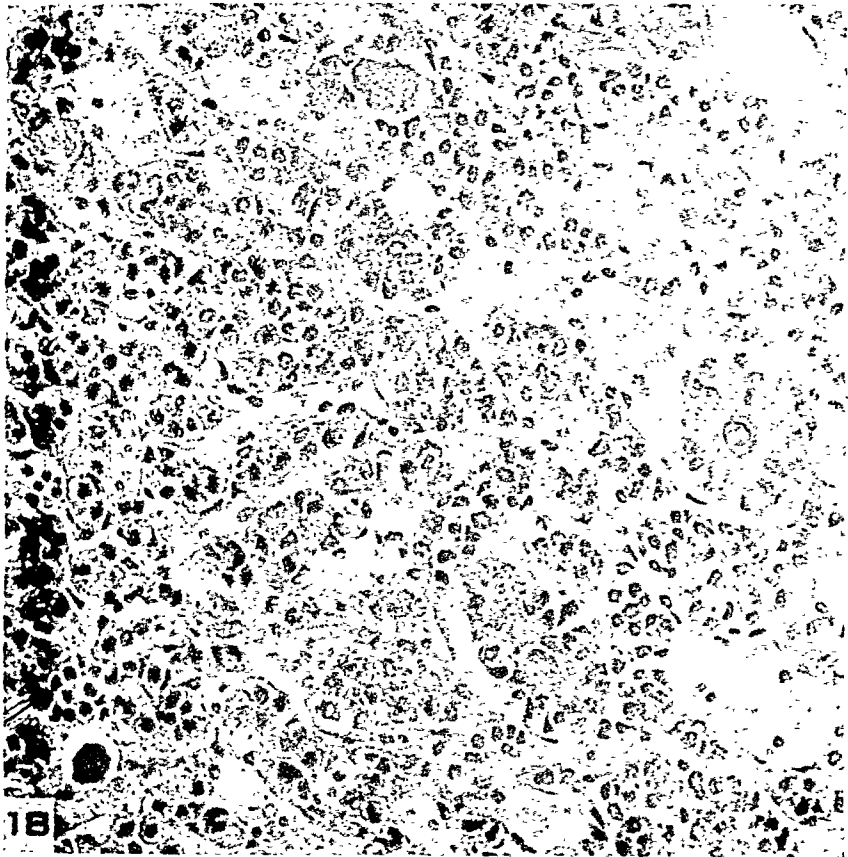


Plaut and Galenson

Concretions in the Anterior Pituitary Lobe

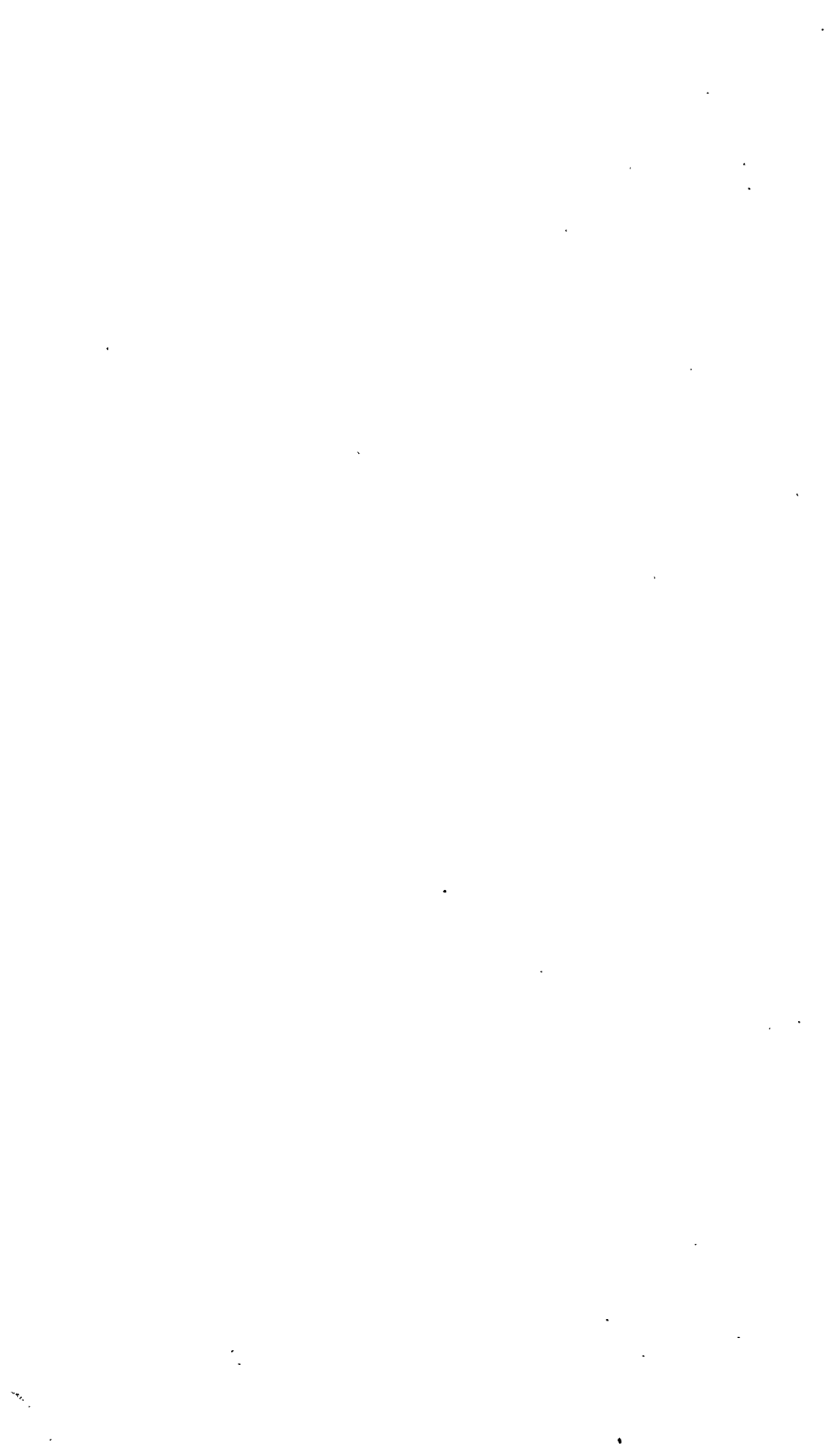
PLATE 44

- FIG. 18. A-134-39, male stillborn, 58 cm. crown-heel length. Intracranial hemorrhage. Four colloid concretions in one microscopic field. One of them is not distinct. $\times 250$.
- FIG. 19. A-134-32, female, 24 years. Rupture of cerebral aneurysm. Lancet-shaped calcific mass in colloid. $\times 670$.
- FIG. 20. A-21-35, female, 3 days old, 33 cm. crown-heel length. Congenital syphilis. Very small colloid concretion with distinct lamination and scalloping of edges. This is a type frequently seen. $\times 960$.
- FIG. 21. A-13-36, female newborn, 50 cm. long. Subdural hemorrhage, aspiration of vernix. Concretion-like mass of varying density without distinct outline; this, perhaps, is a concretion in disintegration. Only parts of the concretion are in focus. (Photomicrograph taken with pinpoint diaphragm.) $\times 1500$.



Plaut and Galenson

Concretions in the Anterior Pituitary Lobe



THE TESTIS IN VITAMIN E-DEFICIENT GUINEA-PIGS *

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Loss of fertility associated with testicular degeneration is a familiar and well studied effect of vitamin E deficiency in the white rat. The very careful work of Mason¹⁻⁴ and others has made clear the underlying histopathology. The change is irreversible;^{5, 6} once effected, the testicular structure and function cannot be restored by vitamin E administration. Daily doses of 0.75 mg. of alpha-tocopherol protect the testis against degeneration.⁷

This striking result of vitamin E deficiency has thus far been demonstrated only in the rat. Bryan and Mason⁸ have shown that mice on vitamin E-deficient diets do not develop testicular degeneration even after 400 days, and this is confirmed by our own experience.^{9, 10} Mackenzie and McCollum¹¹ have found that muscular dystrophy may be produced in rabbits in the absence of testicular degeneration. Only 3 of 11 rabbits used in their experiment received no tocopherol supplement. They were maintained for periods of 49 to 79 days on the vitamin E-deficient diet. While these authors do not draw from their experiments the conclusion that vitamin E is unessential for the integrity of the rabbit's testis, their observations do indicate that the skeletal muscle in this species is more sensitive than is the testis to lack of vitamin. Probably because of the difficulty in raising guinea-pigs beyond maturity on simplified vitamin E-deficient diets, there has been no previous study as to the rôle of vitamin E in preserving the integrity of the testis in this species. Since we have succeeded in maintaining guinea-pigs in good condition for several months after sexual maturity on a diet deficient in vitamin E, the opportunity has been offered to study the condition of the testis in such animals.

METHODS

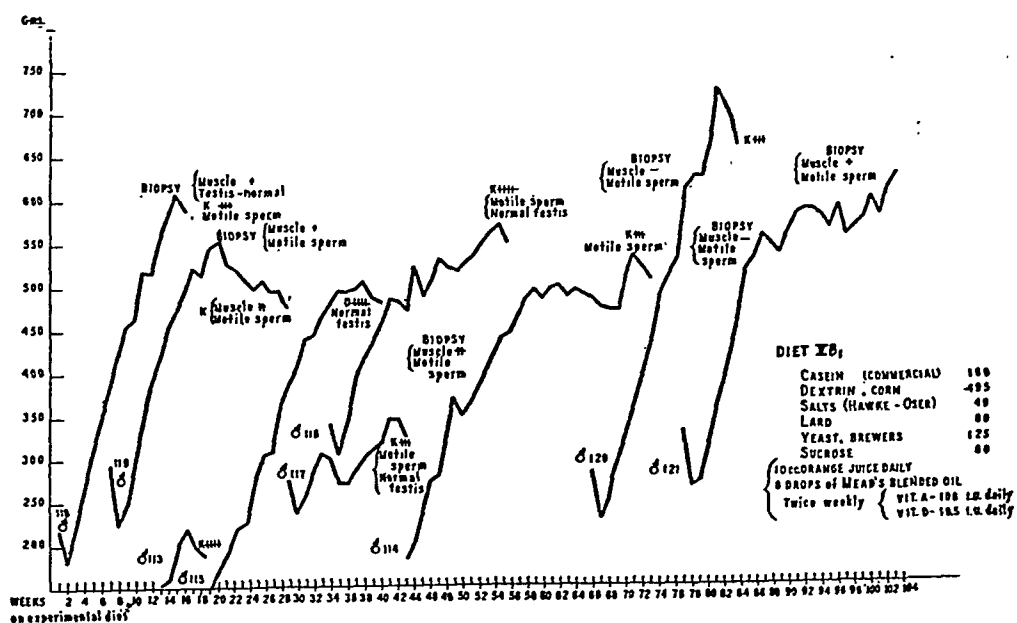
Guinea-pigs were placed on vitamin E-deficient diets soon after weaning. Of 17 animals used in the experiments, 3 received the standard diet V used by Pappenheimer and Goettsch¹² in previous studies on muscular dystrophy, but it was supplemented by aqueous lettuce extract or linseed meal, or both.¹³⁻¹⁵ Cod liver oil was incorporated in the diet. In spite of these additions, growth was poor and

* Received for publication, May 17, 1943.

dystrophy developed between the 60th and 85th days. The testes were normal.

Five other guinea-pigs were given a diet in which dextrin was substituted for cornstarch. In some the diet was treated with ethereal ferric chloride before adding dextrin; in others, the complete diet was treated. All developed severe dystrophy, and the survival period did not exceed 70 days on the diet. The testes, in those animals which survived until after maturity, were normal. A series of 9 guinea-pigs was then given diet V B₁. In the hope of prolonging life, fish liver oil was not incorporated into the diet, but given separately twice weekly by pipette. The diet was mixed into a paste with water, dried with an electric fan, broken into small lumps and fed without additional roughage.

On this diet, the onset of muscular dystrophy was delayed, and the growth of 7 of the 9 animals was excellent, averaging 3.2 gm. daily weight gain for the first 70 days. Eventually all developed typical muscular lesions (Text-Fig. 1).



Text-Fig. 1. Guinea-pigs on a vitamin E-deficient diet.

The vitamin E content of diet V B₁ was tested on 3 pregnant rats, which were placed on the diet immediately after mating. All had resorptions.

The guinea-pigs were sacrificed after they had shown evident symptoms of muscle weakness. The motility of the sperm from vas deferens or epididymis was examined at the time of autopsy, and the testis fixed

in Zenker's fluid for histologic study. In several animals, previous specimens of one testis and muscle were obtained for biopsy, and the motility of the sperm tested.

EXPERIMENTAL FINDINGS

Our observations on diet V B₁ are summarized in Table I. Because of their better growth and longer survival period, the animals in this group have yielded the most informative data.

The testes of 3 animals, killed after 105 days on the diet, presented a normal gross and histologic structure. Motile sperm were obtained from all.

After 130 to 139 days on the vitamin E-deficient diet, 2 of 4 animals showed early degenerative changes in some tubules, from swelling and clumping of the spermatozoa to complete disappearance of spermatozoa and spermatids (Fig. 1). The other 2 animals had normal testes. Motile sperm were present in the epididymides of all.

Guinea-pig 114, from which a normal testis was obtained by hemicastration after 131 days, was killed on the 165th day. The testis then contained a moderate number of degenerated tubules, but motile sperm were still present in the epididymis. Guinea pig 121, having a normal testis on the 84th day, had developed a very advanced atrophy of the remaining testis when killed on the 175th day (Fig. 2). The organ was shrunken, flabby and distinctly brown. Spermatogenesis was absent; the tubules were lined with Sertoli cells, and contained occasional larger elements filled with brownish pigment. The appearance corresponded to Mason's¹ stage V in rats. In spite of the extreme degeneration, motile sperm could still be obtained from the epididymis.

Attempts to prove the fertility of these animals by matings with normal females on stock diet have thus far not succeeded. Seven matings after the males had been from 62 to 112 days on the vitamin E-deficient diet have all been sterile.

The skeletal muscles of all guinea-pigs on diet V B₁ have shown characteristic dystrophic lesions (Figs. 3 and 4).

DISCUSSION

These experiments, like those of Mackenzie and McCollum¹¹ with rabbits, demonstrate that muscular dystrophy in guinea-pigs may be produced while the testis is still histologically normal and elaborating actively motile sperm. They do not bring proof that vitamin E is unessential for spermatogenesis. Testicular degeneration was advanced in the single animal that survived for 175 days, while early degenera-

TABLE I
Muscular Dystrophy and Testicular Findings in Guinea-Pigs on a Vitamin E-Deficient Diet

No.	Days on diet V B*	Initial weight (gm.)	Maximum weight (gm.)	Final weight (gm.)	Muscular dystrophy	Mobile sperm	Testicular structure	Incidental lesions
117	K105	280	342	322	+++	+105 days	Normal	—
118	K105	216	605	535	+++	+96 days +105 days	Normal	—
120	K105	286	730	650	+++	+105 days	Normal	—
115	D130	150	500	365	++++	?	Normal	—
116	K132	340	560	430	++++	+132 days	Swelling and agglutination of sperm (Mason stage I)	Lipoid pneumonia
114	Biopsy 131				++	+131 days	Normal	—
119	K139	296	552	470	++	+139 days	Few tubules degenerated	Hemorrhages over thorax; necrosis of liver
114	K165	180	525	498	+++	+165 days	Moderate number of degenerated tubules	—
121	K175	335	675	635	+	+84 days +163 days +175 days	Normal Complete degeneration	—

* Diet VB₁: Commercial casein, 180 gm.; dextrin (corn), Merck N.F.V. 495 gm.; salts (Hawke-Oser), 40 gm.; lard, 80 gm.; brewer's yeast, 125 gm.; sucrose, 80 gm.; 10 cc. of orange juice daily; 8 drops of Mead's blended fish oil twice weekly, stated to be equivalent to 108 I.U. of vitamin A and 10.5 I.U. of vitamin D.

tive changes in some tubules were observed in guinea-pigs sacrificed at periods from 130 to 165 days.

In the rat, degeneration of the testis is usually present after 40 to 50 days on a vitamin E-deficient diet begun immediately after weaning. From experiments reported in the following article,¹⁶ we have learned that a single small dose of tocopherol given to young rats on vitamin E-deficient diet during the late nursing period will significantly delay the onset of testicular degeneration. Since our guinea-pigs were suckled by mothers on a stock diet containing vitamin E, the late appearance of the testicular degeneration may perhaps be ascribed to this fact. Attempts to gain further information on the influence of this milk factor are being made.

CONCLUSION

Muscular dystrophy developed in guinea-pigs on a vitamin E-deficient diet before the appearance of testicular degeneration. Early degenerative changes were first noted in the testicles after 130 days on the diet, and advanced degeneration was present after 175 days.

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DESCRIPTION OF PLATE

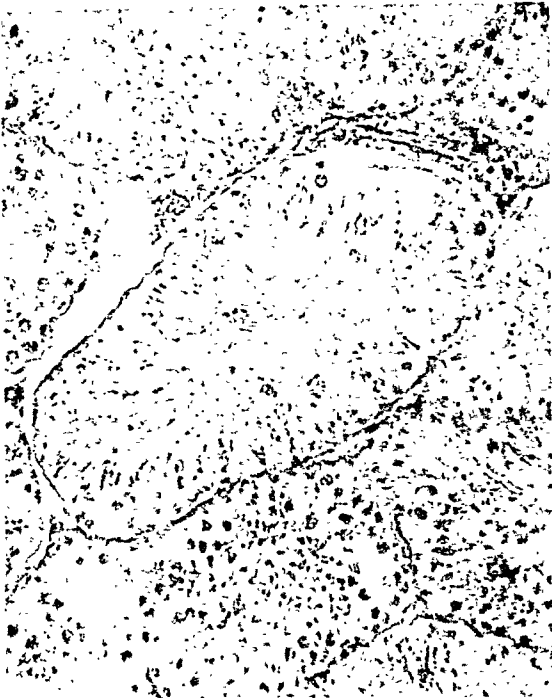
PLATE 45

FIG. 1. Guinea-pig 116. Killed after 132 days on diet V B₁. Early degeneration of testis. Hematoxylin and eosin stain. $\times 190$.

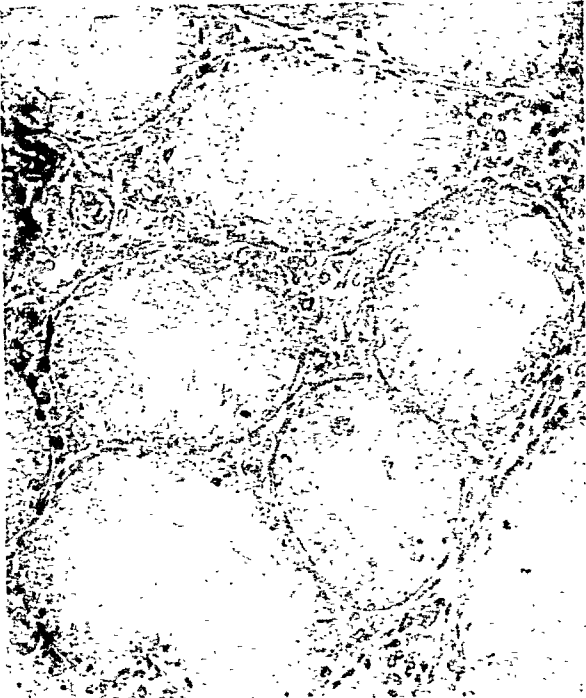
FIG. 2. Guinea-pig 121. Killed after 175 days on diet V B₁. Advanced degeneration of testis. Large pigment cells. Hematoxylin and eosin stain. $\times 190$.

FIG. 3. Guinea-pig 116. Skeletal muscles. Hematoxylin and eosin stain. $\times 90$.

FIG. 4. Guinea-pig 121. Skeletal muscles. Hematoxylin and eosin stain. $\times 90$.



1



2



3



4

Pappenheimer and Schogoleff

Testis in Vitamin E-Deficient Guinea-Pigs

THE PROTRACTED EFFECT OF A SINGLE DOSE OF dl-ALPHA-TOCOPHEROL ACETATE UPON THE TESTES OF RATS ON VITAMIN E-DEFICIENT DIET *

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In studies of the oxygen consumption of young male rats on a vitamin E-deficient diet, it has been found that a single dose of *dl*-alpha-tocopherol acetate given on the 15th day of life is followed by prolonged lowering of total oxygen consumption as compared with untreated litter mates. This effect is continued until the onset of sexual maturity.¹

This paper is concerned with a similar protracted effect of a single dose of tocopherol, given to rats on the 15th day, upon postpubertal testicular degeneration.

METHODS

The mother rats were maintained from the time of weaning on a vitamin E-deficient diet which consisted of: casein (commercial), 320 gm.; cornstarch, 400 gm.; lard, 220 gm.; yeast (baker's dried), 100 gm.; salts (Hawke-Oser), 40 gm.; fish oil (Mead's blended), 20 gm. During lactation, 100 gm. of yeast were added to the diet.

When mating was positive, the litter was assured by protecting the mother with 50 drops of wheat germ oil, given within 5 days after mating. To the treated rats, *dl*-alpha-tocopherol acetate (Hoffmann-La Roche) was given by mouth. Dose and day of administration are stated in the tables. In order to make the tocopherol inaccessible to the untreated rats, they were separated from their litter mates for several hours after the administration. Controls on a Rockland pellet diet † supplied data for normal testicular weights. Comparison in individual experiments was always between treated and untreated litter mates; however, the data given in the tables represent mean values derived from different litters.

The right testicle was removed at various ages under ether narcosis; sperm from the vas deferens were examined in Locke's solution for motility or evidence of degeneration, and a histologic study was made of the testis. In grading the lesions, we have followed the stages de-

* Aided by a grant from the John and Mary R. Markle Foundation.

Received for publication, May 17, 1943.

† A commercial product containing ground yellow corn, ground hulled barley, ground hulled oats, ground whole wheat, soy bean meal, meat scraps, powdered whole milk, alfalfa meal, NaCl (not iodized), precipitated chalk (CaCO₃).

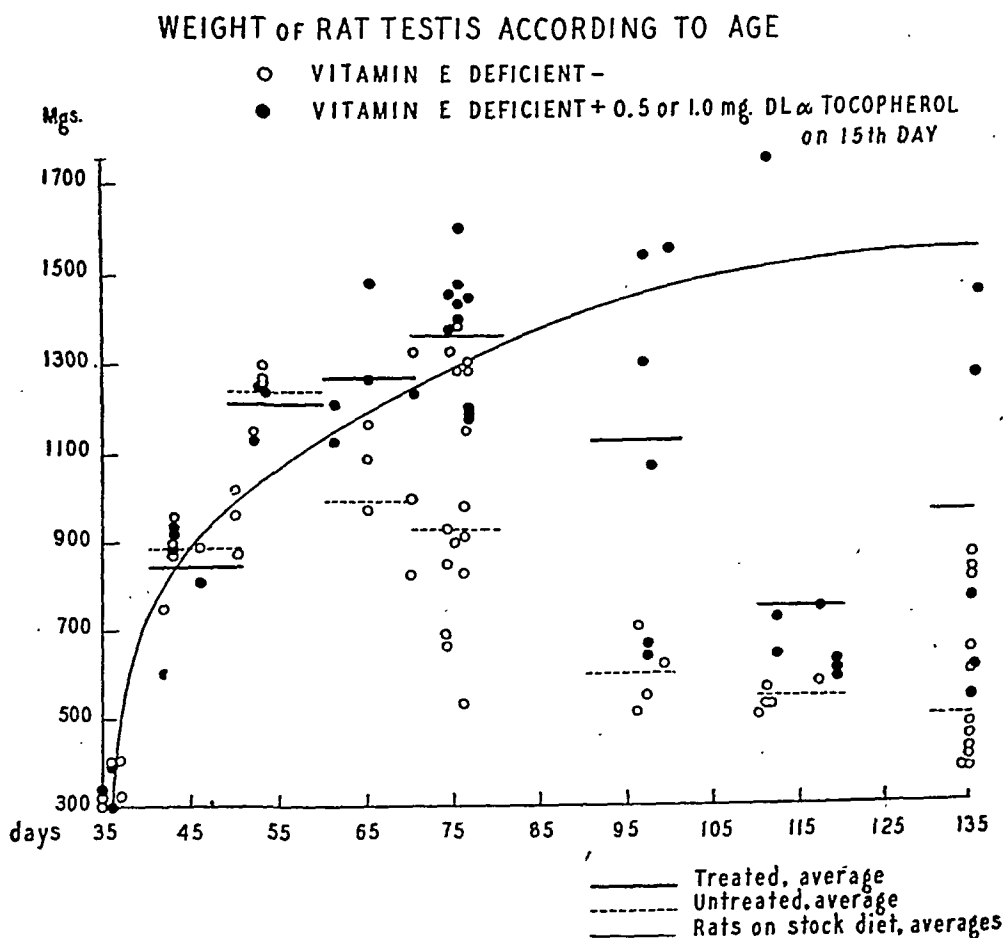
scribed by Mason.² After a further period of observation, the second testis was removed, also under ether anesthesia, and the animal killed.

EXPERIMENTAL FINDINGS

Data upon the weights of one testis at various periods after the administration of 0.5 or 1.0 mg. of *dl*-alpha-tocopherol on the 15th day are given in Text-Figure 1, in which are recorded also the weights of one testis of the untreated litter mate controls.

It is obvious that during the prepubertal period treated and untreated rats have about the same testicular weights. A striking difference becomes manifest after the 60th day. The testicular weight of the untreated animals declines, at first rapidly, then more slowly, to reach a final average weight of about 500 mg.

The testicular weight of the treated rats continues to increase in completely normal fashion until about the 80th day. In 4 of 8 animals, maintenance of normal weight continued until the 110th day. Although



Text-Fig. 1.

Text-Figure 1 appears to show occasional overlapping in the later age groups, this was not the case when litter mates were compared. The average final weight of the testis in the treated rats at 135 to 160 days was nearly twice as great as that of the untreated controls, although there were wide individual variations.

It is seen that most of the testicular weights of treated rats fall above a curve based on the testicular weights of rats of the same colony on a stock diet.* This is explained by the better growth and heavier body weight of the litter on our experimental diet.

Plotting testicular weights against body weights has given comparable curves, although the treated animals tended to be somewhat heavier than the controls.

Motility of Sperm

The effect of the tocopherol in extending the period of sperm motility is clearly demonstrated. In 2 of the treated animals, mobile sperm were present on the 163rd day. In not a single animal were degenerative changes noted before the 100th day in the sperm obtained from the vas deferens, whereas in the nontreated rats, swelling and clumping of the sperm were observed in half of the cases during the period of 71 to 80 days, and in practically all cases thereafter.

Fertility

A limited number of fertility tests were made. In the age group from 61 to 76 days, 10 matings with normal females on stock diet† yielded 4 positive results. In 3 cases, the young, in all 27, were observed for 3 months, during which time they showed normal behavior and growth. Matings were attempted with 9 untreated litter mates of the same age group. No sperm were found in the vaginal plugs, and all matings were sterile.

Histologic Changes

The prolonged protective effect of the tocopherol was reflected in the maintenance of normal structure beyond the period in which degeneration of the testis becomes manifest with untreated vitamin E deficiency. This is brought out in Table II and in Figures 1 to 6. Not included are the histologic findings in 9 treated and 10 untreated animals examined between the 35th and 50th days, since there was no detectable difference in the testes at this time. Nor is there any evident

* We are indebted to Dr. Herbert Stoerk for these data.

† During the mating period, males and females were given only the vitamin E-deficient diet.

TABLE I
Motility or Degeneration of Sperm in Treated and Untreated Rats

Age (days)	35 to 50			51 to 60			61 to 70			71 to 81			90 to 100			110 to 120			120+		
	No.	Motile sperm	Degen. sperm	No.	Motile sperm	Degen. sperm	No.	Motile sperm	Degen. sperm	No.	Motile sperm	Degen. sperm	No.	Motile sperm	Degen. sperm	No.	Motile sperm	Degen. sperm	No.	Motile sperm	Degen. sperm
Treated with 0.5 or 1.0 mg. α -tocopherol on 15th day	9	Sperm absent		3	3	0	6	5	0	13*	10	0	6	1	0	6	0	4	5	2	1
Untreated	10	Sperm absent		4	3	0	5	0	0	12	0	6	4	0	3	5	0	5	7†	0	1

* The 3 rats with nonmotile sperm had received 0.5 mg. of α -tocopherol. All rats receiving 1.0 mg. had motile sperm.

† Four animals showed complete absence of sperm.

TABLE II
Comparison of Testicular Lesions of Treated and Untreated Rats on a Vitamin E-Deficient Diet

Age (days)	51 to 60			61 to 70			71 to 81			90 to 100			110 to 120			120+		
	No.	I to 0	III to II	IV to V	No.	I to 0	No.	I to 0	III to II	IV to V	No.	I to 0	III to II	IV to V	No.	I to 0	III to II	IV to V
Treated with 0.5 or 1.0 mg. α -tocopherol on 15th day	3	3	—	—	6	6	—	13	12	—	6	3	1	2	5	2	—	3
Untreated	4	4	—	—	5	2	3	12	2	4	4	4	—	—	5	—	1	6

* Mason's^a grading of testicular degeneration:

0 Normal testis.

I Degeneration of spermatozoa.

II Degeneration of spermatozoa and "bead-like" degeneration of spermatids.

III Karyorrhexis of spermatids. Giant cells.

IV Disappearance of giant cells. Degeneration of spermatocytes and spermatogonia.

V Tubules lined with Sertoli cells. Disappearance of all spermatogenic elements.

difference between the 51st and 60th day, corresponding to the onset of spermatogenesis. From this time on, as the table shows, degenerative changes are consistently more advanced in the untreated rats. Even after 121 days, one occasionally finds histologically normal testes in the treated rats.

The lesions were graded without previous knowledge as to whether the individual rat had or had not received tocopherol. When comparisons were made between rats of the same litter, the differences were always consistent.

Effect of Increased Dosage

No systematic study has been made of the comparative effect of varying doses. Through inadvertence, however, 4 rats from three litters received 5 mg. on the 15th day, instead of the usual dose of 0.5 or 1.0 mg. This exercised a more delayed protective effect. In the age period of 90 to 101 days, the average weight of one testis from this group was 1.450 gm. as compared with an average weight of 1.134 gm. in rats which had received the smaller dose. All of the animals had motile sperm, and the testes were histologically normal. At 110 to 125 days, the testicular weight in 4 animals still averaged 1.271, as contrasted with a weight of 0.500 gm. in the untreated controls. Motile sperm were still present in 2, and microscopic examination showed only very early degeneration (Figs. 7 and 8).

Influence of Age at Which Tocopherol Was Administered

It has been shown that tocopherol given during the early period of lactation is relatively ineffective in preventing the onset of muscular dystrophy.³ This raised the possibility that it might be equally ineffective in delaying the postpubertal testicular degeneration. Experiments bearing on this point are summarized in Table III, from which it is obvious that there is no protective effect whatever when the tocopherol is given in the early lactational period.

Even more interesting is the fact that administration of 1.0 mg. of alpha-tocopherol on the 29th or 30th day—that is to say, immediately after weaning—is less efficacious than when it is given on the 15th day. This is clear from the observations presented in Table IV. Although there is a definite protective effect, it is distinctly less than when the tocopherol is given on the 15th day; and in some litters, the weight of the testis of individual untreated rats exceeds that of the controls.

DISCUSSION

These observations indicate that a single dose of 0.5 or 1.0 mg. of dl-alpha-tocopherol acetate given on the 15th day of life produces a

TABLE III
Influence of 1.0 mg. dl-Alpha-Tocopherol Acetate Administered on the 6th to 8th Day of
Life on Postpubertal Testicular Degeneration

Age (days)	No.	Average wt. of 1 testis (gm.)	Motility of sperm	Degeneration of sperm	Histologic changes (Mason ³)		
					0 to I	I to III	IV to V
Treated	71-80	1.106	2	5	3	8	1
Untreated	71-80	1.177	0	0	—	3	—
Treated	90-100	0.608	0	8	—	—	12
Untreated	90-100	0.643	0	3	—	—	3

TABLE IV
Difference in Effect Between a Single Dose of dl-Alpha-Tocopherol Acetate Administered
on the 15th or on the 29th to 30th Day of Life

	Age (days)	No.	Average wt. of 1 testis (gm.)	Motility of sperm	Degeneration of sperm	Histologic Changes (Mason ³)		
						0 to I	I to III	IV to V
Treated with 1.0 mg. α-to- copherol, 29th or 30th day	71-80	11	1.240	4	0	6	3	2
Treated with 0.5 or 1.0 mg. α- tocopherol, 15th day	71-80	13	1.362	10	0	12	1	0
Treated with 1.0 mg. α-to- copherol, 29th or 30th day	90-100	10	0.774	0	8	1	2	7
Treated with 0.5 or 1.0 mg. α- tocopherol, 15th day	90-100	6	1.134	1	0	3	1	2

significant retardation of postpubertal testicular degeneration in rats maintained on a vitamin E-deficient diet. In agreement with the findings of Mason,⁴ we can detect no effect during the developmental period. The onset of spermatogenesis is not delayed in the vitamin E-deficient rats, and the spermatozoa for a short time exhibit normal motility. Beginning at the 60th day, however, there is sharp divergence in the behavior of the testis in treated and untreated rats. The continuing effect of the single early dose of tocopherol is reflected in the greater weight of the testes, in the conservation of sperm motility, in the percentage of fertile matings, and in the histologic structure of the organ. This is consistently true, in spite of wide individual variation in the degree of degenerative change at any given period. A still more evident protection is obtained when the dose is raised to 5 mg.

In contrast to this striking protective effect of tocopherol when given on the 15th day is the complete lack of it when the vitamin is administered on the 6th to the 8th day. This is perhaps less surprising in view of the fact that the early administration fails also to protect against the occurrence of muscular dystrophy.

In the experiments of Mason,⁴ the mother and infant rats were transferred on the 14th day from a stock diet containing three times the required amount of vitamin E to a vitamin E-deficient diet. Under these conditions, histologic signs of testicular degeneration began between the 65th and 70th days. This corresponds closely to what has been observed by us in untreated animals. Since Mason's rats presumably received a certain amount of vitamin E during the first 2 weeks of the nursing period, it would seem that a deficiency during the third week is of critical import, and that, as in our experiments, the provision of vitamin E during the early lactational period will not arrest or delay subsequent testicular degeneration. That the third week of lactation is a critical one is further borne out by the fact that when tocopherol is given after weaning it is less effective than when given on the 15th day.

The difference in the average weights of testes between treated and untreated litter mates at the age of 71 to 80 days is thus greatest in those receiving tocopherol on the 15th day, less in those receiving it on the 29th or 30th day, and entirely absent when it is given on the 6th to 8th day. The figures are 0.435 gm., 0.329 gm. and minus 0.061 gm., respectively.

Since over half of the rats treated on the 29th or 30th day had shown previous clinical evidence of muscular dystrophy, it is interesting to inquire whether this may have had a deleterious influence upon the

testicular changes. This is definitely not the case. There is no difference in absolute or relative testicular weights at the age of 71 to 80 days between the animals with and without clinical signs of muscular disease. The lack of correlation between symptoms of muscular disease and testicular degeneration is true also of the untreated animals.

CONCLUSIONS

1. Administration of a single dose of 0.5 or 1.0 mg. of *dl*-alpha-tocopherol to the offspring of vitamin-depleted mother rats delays the onset and retards the course of postpubertal testicular degeneration.
2. Administration of 5 mg. on the 15th day produces a still greater protective effect.
3. Administration of 1 mg. on the 6th to 8th day is without effect.
4. Administration of 1 mg. on the 29th to 30th day affords less protection than when given on the 15th day.

We are greatly indebted to Dr. R. D. Shaner of Hoffmann-La Roche, Inc., Nutley, N. J., for the tocopherol used in these experiments.

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DESCRIPTION OF PLATES

PLATE 46

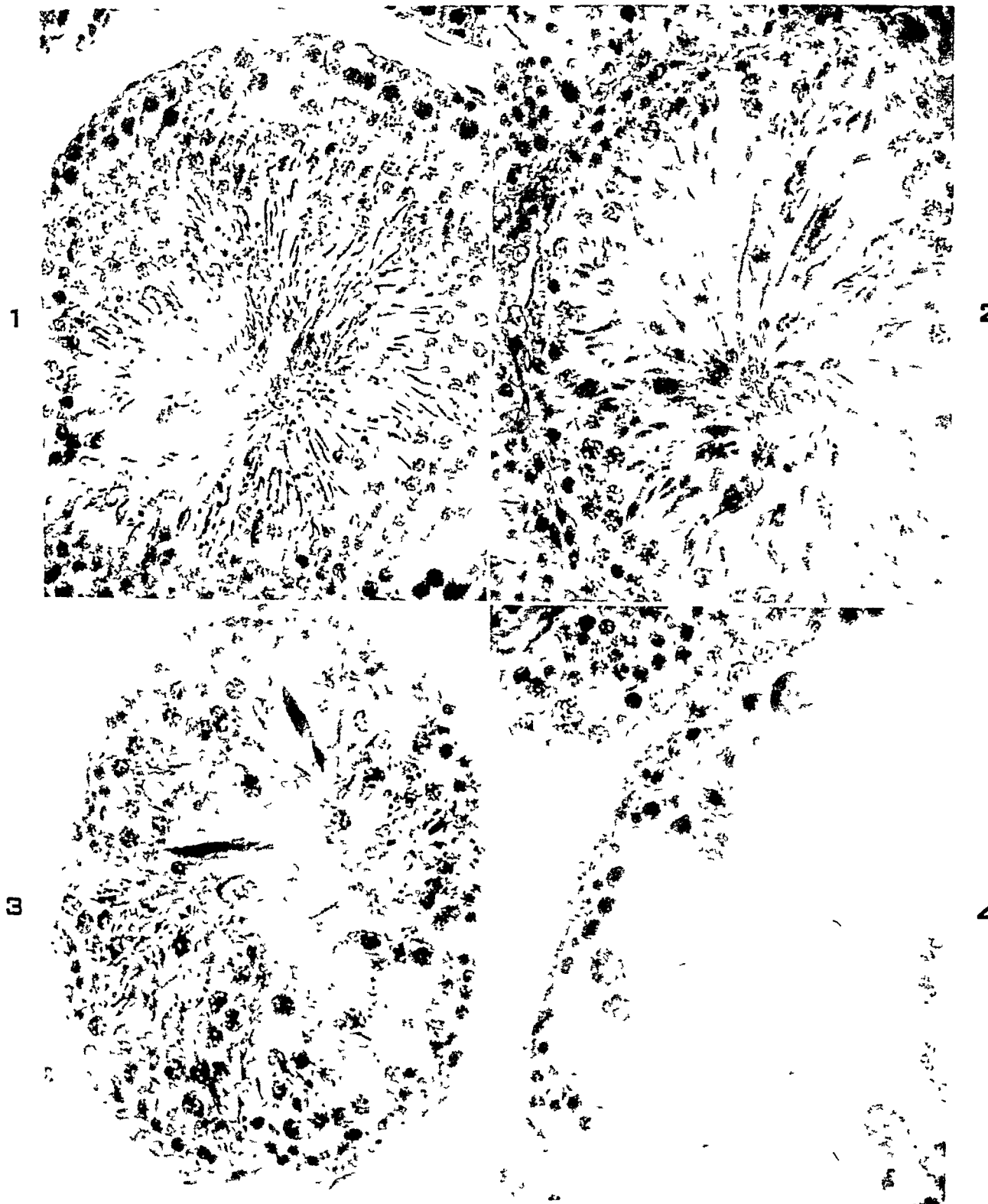
Each pair of figures, beginning with Figures 1 and 2, represents testes from litter mates. Sections are stained with Weigert's iron hematoxylin and eosin stain. $\times 490$. See Table II for Mason grading.

FIG. 1. 65 days. 1 mg. *dl*-alpha-tocopherol on 15th day. Testicular weight, 1.482 gm. Mason stage 0.

FIG. 2. 65 days. Untreated control. Testicular weight, 1.086 gm. Mason stage I.

FIG. 3. 75 days. 1 mg. *dl*-alpha-tocopherol on 15th day. Testicular weight, 1.378 gm. Mason stage I.

FIG. 4. 75 days. Untreated control. Testicular weight, 0.936 gm. Mason stage III.



Kaunitz, Pappenheimer and Schogoleff

Effect of *dl*-Alpha-Tocopherol Acetate upon Testes

PLATE 47

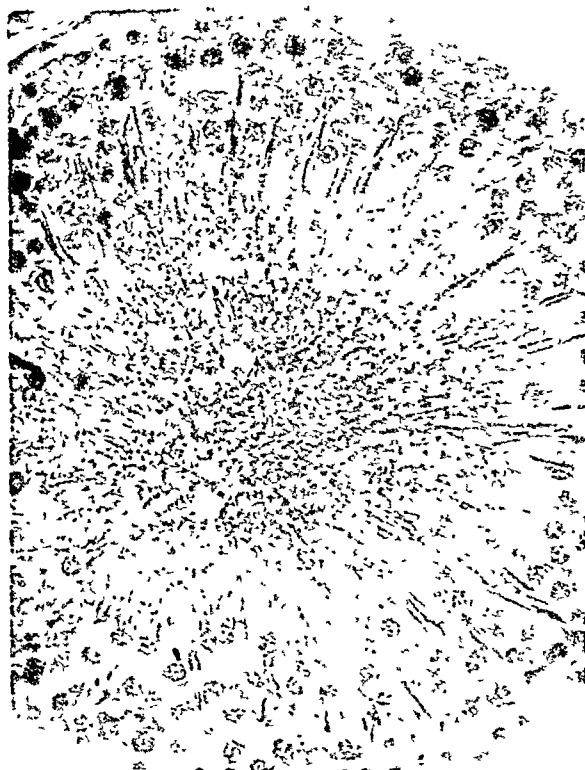
FIG. 5. 97 days. 0.5 mg. *dl*-alpha-tocopherol on 15th day. Testicular weight, 1.071 gm. Mason stage 0.

FIG. 6. 97 days. Untreated control. Testicular weight, 0.549 gm. Mason stage V.

FIG. 7. 121 days. 1 mg. *dl*-alpha-tocopherol on 15th day. Testicular weight, 1.491 gm. Mason stage I.

FIG. 8. 121 days. Untreated control. Testicular weight, 0.594 gm. Mason stage V.

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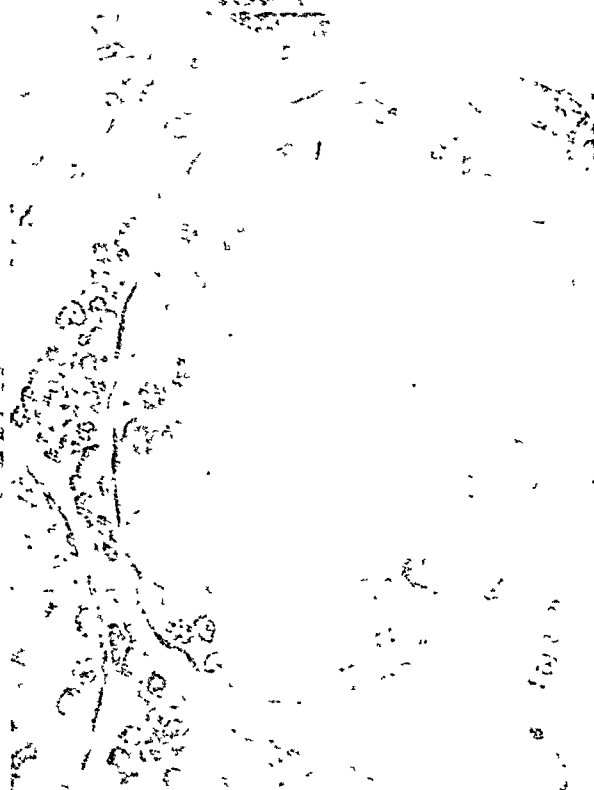
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8



Kaunitz, Pappenheimer and Schogoleff

Effect of *dl*-Alpha-Tocopherol Acetate upon Testes

CHRONIC EQUINE ENCEPHALITIS *

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As a result of recent investigations, it has become evident that of all the forms of acute encephalitis, equine encephalitis, especially the western strain, produces the most characteristic alterations in the brain. Many investigators accept these changes as pathognomonic of this disease even in the absence of further corroborating evidence (Baker and Noran,¹ Weil and Breslich²). During the past few years evidence has accumulated indicating that in this disease permanent and progressive residual lesions may result, especially in children. Most of the recorded cases have been limited to clinical reports in which the symptoms and signs have been strikingly similar from case to case. The most constant manifestations have consisted of epileptiform seizures, progressive mental deterioration and enlargement of the ventricular system as demonstrated by pneumograms. The structural changes responsible for such a picture were unknown until a recent publication from this laboratory.³ The case described was that of a child, 3½ years old, who died approximately 3 years after an attack of equine encephalitis, and who, throughout the course of illness, showed a very high neutralizing titer against the western equine virus. The brain presented most unusual findings. We had never observed similar changes in any other neurologic disorder and to us these changes appeared to be pathognomonic of chronic equine encephalitis. These changes consisted of an extensive cystic degeneration of various selected regions of the cerebral hemispheres. The involved areas were replaced by numerous cavities separated merely by thin layers of gliotic brain tissue. A large portion of the brain showed marked ganglion cell alterations with patchy and diffuse glial proliferation. The most striking features were the vascular changes which consisted of endothelial proliferation and extensive vascular calcification even to the extent of completely occluding some of the vessel lumina. Focal areas of demyelination, so characteristic of the acute illness, also were observed. Although no single feature listed was in itself diagnostic of this condition, the combination of gross and microscopic findings certainly was unique and suggestive of illness of a new type.

Shortly after our original publication on this subject, another case

* This study was aided by a grant from the Research Funds of the Graduate School of the University of Minnesota Medical School.

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came to my attention in which the pathologic findings were identical with those observed in our proved case of chronic encephalitis. Even though there was no way of identifying this case definitely by means of serum neutralization, still the clinical course and especially the pathologic features were so characteristic as to leave little doubt as to the correct diagnosis.

REPORT OF CASE

R. J. (N1754), a white woman, 49 years of age, died following an accident in which she had been struck by an automobile while crossing a street. She sustained a crushing injury to the chest, compound fractures of the right tibia and fibula, a laceration of the scalp and multiple fractures of the pelvis. Despite transfusions of blood and plasma she remained in shock and expired 26 hours later.

The history of the earlier part of her life was incomplete for the only informant available was a sister 11 years younger than the patient.

At the age of 10 days the patient was known to have developed a severe illness diagnosed as brain fever which produced a paralysis of the left side of the body. Recovery, however, was sufficient to allow her to walk at an early age, but a hemiparesis persisted and the extremities on the left became noticeably atrophic. The left arm was held in a flexed position and the left foot dragged in walking. Nonetheless, she became able to walk for long distances. Her left upper limb remained much more severely involved in spite of the fact that she used it a great deal in an attempt to increase its strength.

Early in her childhood epileptiform seizures appeared and recurred at frequent intervals. They were described as sudden attacks of unconsciousness associated with a tonic spasm of the entire body and foaming at the mouth. They were often considerably prolonged and on a number of occasions inhalations of chloroform were required to halt them. At the age of 25 years these attacks abruptly ceased. Between the ages of 30 and 40 years, however, three apoplectiform attacks made their appearance. These were characterized by a sudden loss of consciousness of about 24 hours' duration followed by a protracted period of profound weakness which would persist for about 1 week. Recovery then would be rapid without apparent neurologic residuals.

A number of years before her death she had undergone an enucleation of her left eye following a panophthalmitis, and on another occasion had fractured a clavicle. Menstruation had never occurred. Except for a few minor illnesses of no apparent significance she was always considered to be in excellent health.

She started in school at the age of 8 years. By the time she reached the second grade it was apparent that she was subnormal intellectually and would be unable to continue. She received special tutoring at home for several years with discouraging results, but she did learn to read and write a little. Her accomplishments along these lines, however, were less than those of the informant's 7-year-old son. She led an extremely sheltered life with her relatives. Her chief activity consisted in helping with some of the less complicated household duties. With even the more simple tasks she required constant supervision and was never able to assume any responsibility. Throughout her life her behavior remained at a childish level in that she continued to be interested in playing with dolls and showed an emotional immaturity manifested by occasional temper tantrums.

During the past several years of the patient's life her relatives noticed a gradual decline in her intellectual functions. Her memory for recent events steadily failed so that after only a very brief period she was unable to recall where she had placed certain familiar articles. In addition, various things that were formerly put in a

definite place would be found in different locations every time she used them. Although her mental capacity was always low, her acquaintances felt that a mild but very definite intellectual failure had recently taken place.

Autopsy Findings

There was a laceration of the scalp about 3 cm. in length with slight subcutaneous hemorrhage in that region. Fractures of the second to ninth ribs were found posteriorly on the right, which had caused some laceration of the parietal pleura. There were fractures of the pubis and ileum on the right which had produced a moderate extravasation of blood into the pelvis. There were no fractures of the cranial vault or evidence of dural bleeding.

Gross examination of the brain revealed a marked discrepancy in size between the two cerebral hemispheres. The right, which was normal in appearance, was nearly twice as large as the left. Very striking alterations were evident in the left frontal and temporal lobes. The entire left frontal lobe was remarkably shrunken and atrophic, its tissues appearing thin, opaque, and fluctuant to palpation. Only in scattered areas were remnants of the former convolutional pattern discernible. Except for a small portion of the anterior pole, there was a complete destruction of the left temporal lobe. This region of the hemisphere was represented merely by a small depression under the parietal lobe which was covered by a thin layer of fibrous, structureless tissue. The anterior and posterior central gyri, as well as the parietal and occipital lobes of this hemisphere, demonstrated a normal convolutional pattern although the individual gyri were smaller than the corresponding convolutions on the right. The left anterior cerebral artery was notably smaller than that on the right. Otherwise the cerebral arteries disclosed no abnormalities. The brain stem and cerebellum appeared normal.

Coronal sections evidenced an almost complete destruction of the left frontal lobe which was replaced by numerous small cysts covered by a thin rim of fibrous tissue (Fig. 1). In only a few very small disseminated areas were foci of brain tissue recognizable and even in these identification was questionable. The entire left lateral ventricle was considerably dilated. This dilatation was most marked anteriorly where it appeared to be the result of extensive tissue destruction. The basal ganglia of this hemisphere were displaced downward but displayed a normal architecture. The left thalamus, however, was definitely smaller than that of the opposite hemisphere. With the exception of the anterior pole, the left temporal lobe had been converted into a thin fibrous membrane which in places was semitranslucent. In the adjacent

portion of the left occipital lobe were numerous tiny cystic areas. The right cerebral hemisphere as well as the brain stem and cerebellum showed no gross variations.

Microscopic sections revealed a similar picture in the left frontal and the left temporal lobes. There was an extensive replacement of the parenchyma in these regions by numerous glia-lined cysts of various sizes. Many of the cavitations contained scattered fat-granule cells and were traversed by strands of intertwining neuroglial and mesodermal elements. A few of the very small cystic formations had undergone a relatively complete glial repair. The cysts were frequently separated by very thin strands of gliotic tissue and were covered merely by a thin band of cortex (Fig. 2). The cortical gray matter disclosed a complete devastation of its ganglion cells and all but the outer layers were replaced by the cystic degeneration. The remains of the underlying white substance showed a relatively complete destruction of myelin sheaths and axis cylinders. Throughout all this devastated tissue there was a profound proliferation of the macroglia. In many regions the gliosis was principally cellular with very little production of astrocytic fibers, while in other areas the altered tissues were completely replaced by a dense meshwork of coarse, intertwining neuroglial fibers. In a few areas dense, acellular scars had resulted. Scattered diffusely through this proliferating glial tissue were numerous globules of calcification, often arranged in focal collections. These globules were comprised of densely packed calcium granules corresponding in size to the small cortical blood vessels. Corpora amylacea were only occasionally observed.

The small blood vessels of the frontal and temporal regions, especially the arterioles and capillaries, demonstrated swelling and proliferation of their lining endothelium, often with relatively complete occlusion of the lumen. Often all of the elements of the vessel wall had proliferated, resulting in extreme thickening of the wall and obliteration of the lumen. A large number of these vessels had become hyaline, creating an appearance of a fibrous mass. In vessels of this latter type, calcium granules were found most often around the intima but often replaced the entire vessel so that the vascular structure could not be identified. The small veins displayed considerable adventitial proliferation and many were encircled by mononuclear cells, mainly lymphocytes. In numerous small vessels this mononuclear infiltrate formed thick collars filling the perivascular spaces. Focal collections of leukocytes, consisting of both lymphocytes and polymorphonuclear leukocytes, were also found in a few disseminated areas intermixed with a small number of astrocytes.

In the regions of the cerebrum that were grossly normal, less prominent variations were seen. These were most pronounced in regions adjacent to the areas of gross tissue destruction, but were also found throughout the entire cerebrum. Alterations of the cortical neurons had occurred only in disseminated areas. The most constant neuronal change consisted of pyknosis and shrinkage of the cell body, but a few cells were swollen and chromatolytic with occasional ghost cell formations. These alterations frequently occurred in the vicinity of a small vessel showing extensive endothelial proliferation with occlusion of the lumen. Frequently there was a dropping out of some of the neurons and in certain cortical areas there was an increase in astrocytes. Scattered throughout the gray matter of the occipital region there were, in addition, large globules showing concentric rings of calcification reminiscent of the vascular calcification previously described.

Within the white matter of the grossly normal regions of the hemispheres, there were numerous scattered areas of focal demyelination which were generally not associated with any glial increase. These were irregular in outline and quite sharply demarcated from the surrounding tissue. In the subependymal region the demyelination tended to be more diffuse. Glial nodules, although not common, were occasionally seen. A few subcortical vessels displayed a perivascular lymphocytic infiltrate, while the walls of a few others were invaded by neutrophils. This latter change was seen only in selected instances.

In all of the basal nuclei nerve cell alterations were prominent. The ganglion cells were frequently swollen and their cytoplasm contained relatively large amounts of granular lipofuscin pigment. The nuclei were eccentric and often fragmented. Ghost cells were not uncommon. Large and small focal areas of demyelination were found. In these areas the nerve cells were shrunken, pyknotic and even fragmented. A few glial nodules were seen in the pallidum. Occasional perivascular infiltrates were also encountered in the corpus striatum, but they were infrequent.

In the brain stem and cerebellum the alterations were mild and of a patchy nature. Regressive neurocellular alterations were found as well as irregular areas showing myelin degeneration. Well formed collars of lymphocytes filled the perivascular spaces of a few vessels (Fig. 3).

DISCUSSION

It seems fairly evident that the pathologic features in the present case are unusual and correspond in every detail with those already described in a proved case of chronic equine encephalitis. It is felt that such

characteristic cerebral alterations are in themselves sufficient for diagnosis, even in the absence of corroborating evidence such as neutralizing antibodies in the serum or the occurrence of the illness during an epidemic of the disease. Even though equine encephalitis has only recently been definitely identified in both the horse and man, it is well recognized that this disease has existed in this country for many years and the clinical syndrome has been described in many epidemics among horses. In view of the prevalence of this disease, at least among the equine population, it would seem inevitable that human infection should occur, especially since it is now known that man is susceptible to this virus. No doubt many cases of human infection have been occurring for years, but have gone unrecognized because of the lack of adequate means of identification in the laboratory. Since this disease does produce chronic and progressive sequels, we would expect to encounter, at least occasionally, cases in which the brain reveals findings indicative of the original infection.

The present case is most instructive because histologically there appeared to be every evidence, not only of chronic damage, but also of an active acute process as indicated by the foci containing polymorphonuclear leukocytes, the extensive perivascular mononuclear collections and the vascular endothelial increase. That such an active process was still in progress was also strikingly revealed by an analysis of the clinical course of the illness. Certainly both the increasing mental deterioration and the periodic apoplectic seizures pointed to activity. In addition, the disappearance of the epileptogenic focus after 25 years suggested the presence of a progressive destruction of cortical tissue. These observations of a process both clinically and, especially, pathologically active for over 40 years after the onset of an encephalitis are most amazing and strongly influence our concept of virus infections. It would appear that in some virus infections, the recovery from the acute illness merely indicates an ability of the host to prevent the further spread of the virus, but that the noxious agent is not destroyed and is capable of again spreading as soon as the host's resistance is reduced. At least in equine encephalitis, one questions whether the virus is ever destroyed, once it invades the human organism. That this concept may be true is further suggested by the observations of many investigators that in this disease, neutralizing antibodies can be observed in high titers many years after the acute illness.⁴

CONCLUSIONS

1. A case of chronic equine encephalitis is presented.
2. Both the gross and microscopic lesions were identical with those previously described in a proved case.
3. Grossly the brain revealed an extensive cystic degeneration of the left frontal and temporal lobes. Microscopically there was a widespread parenchymal degeneration with focal areas of inflammatory infiltrate. Many vessels were occluded by an endothelial proliferation and deposition of calcium.
4. A pathologic picture is described which is seen in no other condition and is, therefore, regarded as pathognomonic for chronic equine encephalitis.
5. The histologic evidences of active inflammation as well as the clinical course demonstrate that the western virus may remain active for many years in equine encephalitis.

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[*Illustrations follow*]

DESCRIPTION OF PLATE

PLATE 48

- FIG. 1. A coronal section demonstrating the extensive destruction of the left frontal lobe. The ventricle is extremely dilated and the remaining tissue harbors large cystic areas.
- FIG. 2. A thin band of frontal cortex overlying a large cystic area. There is a complete devastation of ganglion cells and a diffuse glial proliferation. Small globules of calcification are scattered throughout the cellular areas. Hematoxylin and phloxine stain. $\times 150$.
- FIG. 3. A perivascular accumulation of lymphocytes resembling that seen in acute equine encephalitis. Hematoxylin and phloxine stain. $\times 375$.

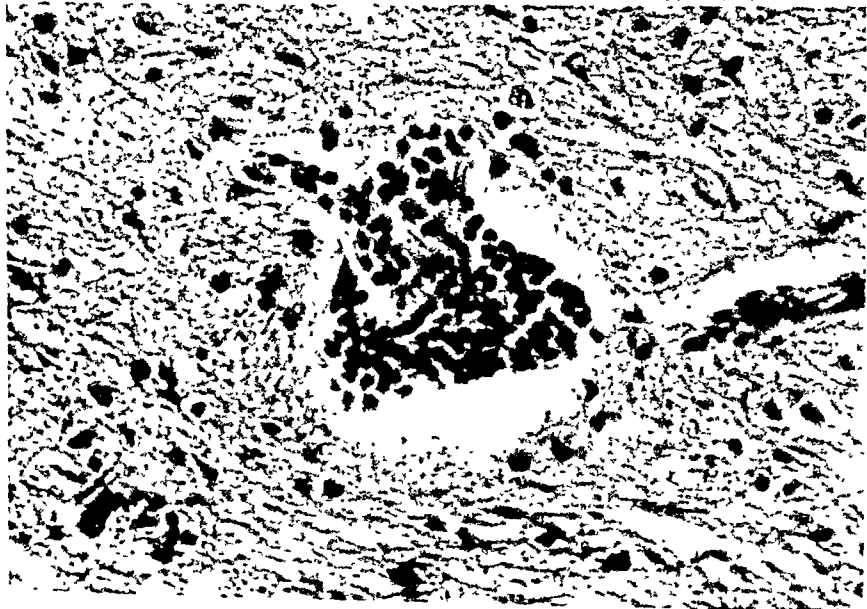
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MENINGOCOCCAL ENDOCARDITIS IN IMMUNIZED HORSES*

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The essential condition in the pathogenesis of bacterial endocarditis is one of localization of the incitant. Bacteria, irrespective of any special selectivity of the microorganisms for the particular tissue, may passively localize on valvular endothelium that has been predisposed by some injury. After sensitization to an antigen, an animal develops a hyperergy to subsequent invasion of that antigen, or even other antigens, that is manifested by morphologic changes in the endothelium and certain other tissues. The injured tissues are thus predisposed to bacterial localization.¹⁻⁵ The animal under immunization in various stages of sensitization presents precisely such conditions for study.

Among 110 horses under immunization with meningococci, 14 developed endocarditis. All had been given living cultures of meningococci of groups I-III and II intravenously.⁶ One horse had previously received diphtheria toxin and 3 horses had also been injected with meningococcal filtrate, either subcutaneously or intravenously, at some time during immunization.

CLINICAL RÉSUMÉ

A review of the records of the 14 horses with endocarditis and the clinical and autopsy notes by Drs. Charles A. Griffin and Cyrus P. Brose, Veterinarian-Bacteriologists on the staff, are briefly summarized to outline the significant symptom-complexes and anatomic changes found at autopsy. The 14 horses varied in age from 7 to 26 years, averaging 17 years, and were under immunization for from 5 to 26 months, an average of 14.5 months.[†] Following the injections, all horses that received living microorganisms had variable reactions characterized by trembling, dyspnea, weakness, tachycardia, and weak pulse. Injections of toxic culture filtrates usually induced fever and subcutaneous edema. The animals developing endocarditis presented a progressive symptom-complex of fever, weakness, loss of weight, subcutaneous edema, and weakness of the extremities. In 9 of the 12 animals with fever, meningococci were obtained in the blood cultures

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† The entire group of 110 horses were of the same age range. Fifty-four horses (50 per cent) were under immunization for from 6 to 9 months and 46 (40 per cent) from 20 to 24 months. Four horses were immunized for from 36 to 48 months and 1 animal has been yielding serum of high antibody titer for 10 years.

taken when the febrile reaction failed to subside. The febrile reactions with bacteremia persisted from 5 to 105 days, averaging 38 days, when the horses either were destroyed or died. With few exceptions, the horses with bacteremia had produced sera of high potency. A cardiac murmur was heard in 8 horses, appearing as early as the 5th month and as late as the 30th month of immunization and persisting as long as 100 days. Nine animals had subcutaneous edema exclusive of that induced by injections of filtrate. Cyanosis, epistaxis, and excessive perspiration were each encountered once. Weakness of the hindquarters occurred in 10 and definite lameness appeared in 5 animals.

Autopsies were performed on all 14 horses. Tissue was fixed in Zenker's fluid and formaldehyde solution. Sections were stained with hematoxylin and eosin and with phosphotungstic acid hematoxylin and, for demonstration of microorganisms, by the Brown-Brenn method⁷ and with carbol thionin.

GROSS ANATOMIC OBSERVATIONS

All 14 horses had endocardial valvular lesions of the left side of the heart. The right side was not involved. In twelve hearts, the aortic valve bore vegetations varying from a small verruca to an ulcerative mass, 3 cm. in diameter. All of the cusps of three aortic valves were involved. The mitral valves of three hearts had vegetations and in three more hearts the mitral cusps were thickened and edematous. In 12 horses, cultures of meningococci were recovered from affected valves. Adherence of a mitral vegetation to the ventricular wall and a vegetation on chordae tendineae were encountered. Neither the symptoms nor even the condition of the horses indicated the extent of the valvular lesion.

The gross pathology of these horses was further characterized frequently by vascular thromboses and accompanying visceral infarction. The autopsy notes record that the following vessels were thrombosed: pulmonary artery, twice; pulmonary veins, twice; renal artery, once; renal veins, twice; splenic artery, four times; splenic vein, once; hepatic artery, twice; hepatic portal vein and tributaries, four times; colic artery, once; and mesenteric artery, four times. Infarcts were observed in the lung, once; in the kidneys, three times; in the spleen, twice; and in the liver, once.

In microscopic sections from one horse, infarcts in the lung, liver, and kidney parenchyma with attendant arterial thrombi were found. Tissue sections from a second horse contained hepatic and renal arterial thrombi, while splenic and renal infarcts were demonstrated in stained tissues of a third animal.

Two hearts presented definite myocardial hypertrophy, and gross myocardial scarring was noted in one cardiac apex. Pneumonic consolidation was found at autopsy in three horses. Enlargement of the spleen, a frequent development in immunized animals, was found only four times. There was a varying amount of liver damage. Twice the hepatic capsule was ruptured and this was accompanied in one horse by fatal hemoperitoneum and in another by massive subcapsular hematoma. With thrombosis of the colic artery, gangrene of the colon occurred. The kidneys were usually swollen, edematous and pale. Subcapsular hemorrhages were frequent and purulent material was found in the pelvis three times.

RESULTS OF BACTERIOLOGIC STUDIES

As a result of study of cultures recovered from these horses from the blood stream or at autopsy, it was reported⁶ that: "Meningococci were isolated from eleven horses which developed endocarditis during immunization against several meningococcal strains of groups I-III and II. The cultures from ten horses were group I-III and those from eight of these animals resembled closely one of the stock strains used in immunization. The culture from the eleventh horse was mixed, but group-II microorganisms predominated. No changes occurred in the agglutinative or precipitative activities of cultures isolated repeatedly from individual horses. Of those tested, the cultures were, in general, of low virulence for mice, lacked well-defined capsules, and possessed a marked capacity to survive in sodium-chloride solutions."

Meningococci of group I-III were also recovered from two other horses.

HISTOPATHOLOGIC FINDINGS

Heart

Valves. Although the predominant lesion on the valves was a macroscopic ulcerative vegetation, the endocardium exhibited certain characteristic changes: initially, a swelling of the endothelial cytoplasm with swelling and elongation of the nuclei. This endothelial edema gave rise to a separation of the endothelial layer from the subendothelial tissue leading to wrinkling, fragmentation and, finally, desquamation of the endothelium. In some areas, gram-negative diplococci could be demonstrated on the swollen endothelium among the desquamating cells and in the superficial portion of edematous subendothelial tissue. The denuded surface occasionally showed a fibrin layer containing endothelial cells, blood elements and bacteria. Buds of endothelial cells were noted in the reparative processes of this denuded area. These

manifestations were more strikingly demonstrated in a horse that had been treated with sulfanilamide, which prolonged the course of the disease, clearing the bacteremia which reappeared regularly on abandoning treatment.

In other areas, a bare subendothelial layer showed fibroblastic proliferation with fibroblasts tending to form a pseudopalisade surface layer of spindle-shaped cells with fibrillary processes separated by intercellular edema. This reaction often presented a burgeoning of fibroblasts forming papillary projections. The fibroblastic tissue was infiltrated by numerous mononuclear cells. This pseudopalisade layer of tissue, likewise, may be the repository for circulating blood elements and bacteria.

The fibroblastic wall, reparative and defensive, further changed into a loose fibrillary structure with atrophic cells through a process resembling mucoid degeneration. The fibrous verrucae became covered with endothelium or accumulated fibrin and blood elements. Some were hyalinized, vascularized and fibrosed with resultant scarring of the valve.

At any stage from the initial edematous endothelium to the scarred verruca, successful bacterial colonization, with or without antecedent thrombotic processes, may give rise to the well known ulcerative vegetation. Frequently the transformation from swollen endocardium to ulcerative vegetation was seen as one progressed from the base of the valve to the distal vegetative lesion. In many places the transformation of the pseudopalisade layer of subendothelial tissue into granulation tissue occurred adjacent to the thrombotic vegetation proper. The fibrochondroid plate was edematous and there was moderate to marked thickening of the arteriolar walls due to medial and intimal hyperplasia. However, hemorrhagic foci of the endocardium and of the blood vessels of the valves, such as Wadsworth⁸ noted in horses under pneumococcal immunization, were not observed in these valves. No thrombosis of the blood vessels of the valves was seen and no intravascular bacteria. Bacterial stains revealed bacteria only on the surface of the damaged valve or in the superimposed thrombotic mass. Microorganisms were not seen in the depths of the subendothelial tissue. The advanced vegetation consisted of a fibrin mesh containing disintegrating erythrocytes, cell debris, blood pigment, and irregular strata and clumps of polymorphonuclear leukocytes and gram-negative cocci. On the surface of the vegetation, colonies of bacteria were large and numerous; this is in contrast to the paucity of pneumococci Wadsworth⁸ observed in vegetations of pneumococcal endocarditis. The bases of these meningo-

coccal vegetations showed hyalinization and fibroblastic invasion. This granulation tissue contained occasional small abscesses and considerable round-cell infiltration.

Myocardium. The ventricular and auricular myocardial damage varied. Interstitial edema was not uncommon. Old, minute, fibroid infarcts, scattered areas of myocardial degeneration and atrophy with fibrous replacement, and some arteriolar sclerosis were occasionally found. In one horse, an acute, purulent, interstitial myocarditis was observed at autopsy.

Lungs

In the lungs of two horses, arterial thrombi were demonstrated. A large artery was seen to contain a thrombus extending into tributaries and leaving empty distal vessels. The endothelium was swollen, vacuolated and ragged, with some interruption of the media. Occasionally bronchitis, peribronchitis and patchy bronchopneumonia were encountered.

Liver

The hepatic damage varied from a chronic venous congestion to moderately severe parenchymatous degeneration, largely central in distribution. One liver showed a periportal cirrhosis accompanied by bile duct proliferation; one duct containing purulent material in the lumen. Another liver with a large venous thrombus had approximately one-third of the parenchyma destroyed and replaced by a suppurative process and fibrosis. These changes are in general agreement with the observations of Wadsworth, Hyman and Nichols⁹ on the livers of 41 horses immunized with tetanus and diphtheria toxins and with meningococcal, pneumococcal and streptococcal cultures; in fact, they included in their studies of the lipid content of such livers two horses with meningococcal endocarditis (no. 287 and no. 347).

Spleen

There were numerous thrombi and infarcts, and several spleens showed reticular hyperplasia with multinucleated giant cells.

Kidneys

Most pronounced were the severe and general interstitial changes in the kidneys consisting of focal and diffuse infiltrations with mononuclear cells, accompanied by generalized advanced tubular degeneration with a variety of casts, largely leukocytic, epithelial and erythrocytic. In some kidneys, extensive fibrosis existed. The kidneys of six horses

showed definite glomerular damage. This varied from capillary hyperemia, swelling and vacuolation of the endothelium, exudation and hemorrhage into Bowman's space, to fibrosis and hyalinization of the glomerulus, capsular thickening and crescents. Thrombi of the renal arterioles were found in one animal and ischemic renal infarcts in two horses.*

DISCUSSION

The lesions in the valves of those horses under immunization that developed meningococcal endocarditis appear to correspond in the initial as well as in the later stages with those reported in experimental studies on the development of endocarditis without antecedent mechanical trauma in previously sensitized animals that have been given living microorganisms. Nedzel² and Keefer¹¹ have reviewed the literature on experimental endocarditis. As early as 1919, Wadsworth⁸ described the endocardial valvular lesions in horses under pneumococcal immunization, and, more recently, horses used in serum production were not infrequently found to have endocarditis.^{12, 13} The occurrence of arterial and venous thrombi in these horses supports experimental³ and clinical⁴ observations in which thrombosis has been found to be associated with vascular endothelial changes in the sensitized or immunized subject.

Since damage to the valves and blood vessels occurred in the absence of mechanical trauma, it may well be that the endothelium of such horses is altered in the course of immunization in such a manner that it is a favorable focus for bacterial localization or thrombus formation. The altered endothelium may become more vulnerable to the toxic bacterial products that prepare the way for subsequent colonization of the microorganisms, as suggested by Wadsworth⁸ 25 years ago in his study of endocarditis in horses under pneumococcal immunization. Judging from the type of lesions induced, many bacterial toxins have a selective action on tissues. One group, exemplified by streptococcal toxins, is essentially an endothelial poison and gives rise to hemorrhage in the tissues. As Wadsworth has stated:¹⁴ "Tissue susceptibility, possibly specific sensitization, is the underlying condition determining the action of the toxin of the different streptococci, as was very strikingly illustrated, in one instance, by the development of hemorrhagic purpura in the course of a human infection of several years' duration." Toxic vascular damage is particularly suggested with the pneumococcus for Wadsworth⁸ noted hemorrhagic foci in the endocardium and in the

* Dr. Joseph Schleifstein has made an extensive study of the nephritic changes; they were reported in abstract¹⁰ and will be published.

valvular vessels. Such lesions were not seen in these studies of meningococcal endocarditis. The serum of the horses with pneumococcal endocarditis had a high antibody titer; that of horses with meningococcal endocarditis likewise was generally of high potency.

The normal cardiac valve of the horse contains blood vessels through which bacteria may gain access to the damaged endocardium. It is extremely difficult to demonstrate bacteria morphologically in the blood even though a bacteremia is present. Bacterial stains of these sections failed to reveal intravascular microorganisms; hence the difficulty of excluding access to the endocardium through the blood vessels. However, the distribution of bacteria as observed in these studies suggests localization from the blood bathing the valve surfaces.

Endothelial changes, similar to those observed in horses with meningococcal endocarditis, were noted in a very thin aortic valvular plaque from a horse under pneumococcal immunization. A rabbit, after having only six injections of killed pneumococcal vaccine, had a mitral valve with large edematous endocardial verrucae, as yet devoid of bacterial or thrombotic elements. The altered behavior of host tissues toward specific bacterial antigens frequently leads, first, to a stage of hypersensitivity and, later, to a stage of insusceptibility to infection and immunity, which may fluctuate in the same host. Thus, we have different phases and degrees of susceptibility to infection which must be taken into account in considering the influence of the immunizing process on the development of endocarditis. The early stages should be studied in order to determine the interrelation of endothelial alterations and bacterial endocarditis occurring during immunization of animals.

These observations on the different stages of the development of endocarditis in animals under immunization appear to correspond with those reported by others in experimental and clinical studies. In these horses immunized with the meningococcus, endothelial damage appears to be the primary stage, leading to inflammatory reactions, thromboses and localization of the bacterial incitant. This endothelial damage may be associated with varying stages of susceptibility developing in the course of immunization.

SUMMARY

Among 110 horses under immunization with the meningococcus, 14 animals developed endocarditis; multiple arterial and venous thrombi were frequently found at autopsy. From the histologic studies of the autopsy material of these 14 animals it appears that the initial stage in the development of the endocarditis is edema and swelling of the valvular endothelium with wrinkling, roughening, and finally desquama-

tion of endothelial cells. This leads to inflammatory cellular reaction and a reparative process, or to thrombosis and localization of bacteria that culminates in the advanced ulcerative vegetation. The tissue changes suggest that in the course of immunization alterations may occur in the endothelial tissues, leading to injury that predisposes to bacterial localization and subsequent endocarditis.

I wish to express my gratitude to Dr. A. B. Wadsworth not only for suggesting this study but for his invaluable guidance.

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CULTURAL CHARACTERISTICS OF A HEMANGIOENDOTHELIOMA*

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The hemangioendothelioma is a rare variety of malignant neoplasm characterized by the formation of anastomosing vascular tubes and atypical endothelia. In another communication¹ one of us (A. P. S.) has reported 18 cases of hemangioendothelioma illustrating its variations in growth rate and morphology. One of those cases has been studied by the method of tissue culture and it is our purpose here to describe the details of that investigation. The tumor is of unusual morphological appearance but its behavior *in vitro* leaves little doubt that it represents an authentic variant of this interesting vascular tumor type.

CASE HISTORY

The patient was a colored male, 28 years old. The growth first appeared as a marble-sized lump in the left calf 3 years before operation. It did not seem to increase in size until 9 months before treatment when the calf began to swell and became painful. Aspiration 4 months before had yielded only blood. Examination on admission to the hospital showed a diffuse enlargement of the left calf which measured 47.5 cm. in circumference while the right calf was 36 cm. The swelling seemed to be due to a deep-lying fusiform tumor of vague outline. It was suggested that it lay deep to the soleus muscle. The periosteum of the fibula seemed roughened on x-ray examination, suggesting that the tumor might be attached to it. The left calf felt warmer than the right. Operation was performed on March 13, 1942, under the supervision of Dr. C. D. Haagensen. The tumor was first approached through a posteromesial incision but so much bleeding was encountered when its vicinity was reached that a specimen for biopsy was not taken here but a second posterolateral incision was made. After the lateral head of the gastrocnemius muscle was partly divided and the soleus retracted mesially, it was possible to obtain tissue for biopsy, although bleeding was profuse. A frozen section was interpreted as a malignant tumor but its exact nature could not be stated. Amputation was then carried out through the lower third of the femur. One year later there was no evidence of metastasis or recurrence.

After the leg was dissected, it was found that the flexor digitorum longus and flexor hallucis longus muscles were the site of a tumor which measured 16 cm. from above downward, 13.5 cm. in greatest transverse diameter and 6 cm. from before backward. It was exceedingly vascular and contained large spaces filled with viscous, black, bloody fluid in some areas while elsewhere the relatively homogeneous, soft, pink tissue was speckled with countless tiny red dots. The tumor had also invaded the soleus and peroneus brevis muscle. It was sep-

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arated from the popliteal space by the tibial attachment of the soleus muscle. The bones were not invaded. Photographs of the leg before amputation and of the cut surface of the tumor can be seen in the paper¹ by one of us (A. P. S.) already referred to.

After explantation of sterile neoplastic tissue, portions were fixed in Helly's and Bouin's fluids and in 25 per cent choral hydrate. Hematoxylin and eosin; Masson's aniline blue, acid fuchsin, ponceau trichrome stain; phosphotungstic acid hematoxylin; Laidlaw's silver carbonate reticulin stain and Cajal's silver impregnation were used.

Only after long study with the stains mentioned was it possible to interpret the morphological characteristics of this tumor. It consisted basically of an enormous number of capillary vessels, some of which contained red blood cells, but the majority of which did not. These tended to anastomose one with another and ran at haphazard in every direction. A few were lined by normal endothelia but the majority by larger spindle-shaped tumor cells. These had usually proliferated to such a degree that the vascular lumen was obscured and in ordinary stains one could see only cords or columns of cells running in various directions. It was only when such cords were found directly continuous with tubes containing red blood cells that one could suspect that they were obscured vessels (Fig. 2). This suspicion received confirmation from the silver reticulin stain which showed that the cell columns were enclosed within a capillary reticulin sheath. Between these tubes and solid cords were many other cells of a similar aspect supported by a matted, tangled framework of fine silver-blackened reticulin fibers.

Most of these tumor cells had a relatively mature aspect and mitoses were difficult to find. Their ovate nuclei contained two or more small nucleoli and were sharply defined. The cytoplasm was rather scanty, well defined, faintly acidophilic and slightly granular. At its edges the tumor cells infiltrated the surrounding muscles and aponeurotic tissues by sending out short tongue-like prolongations.

From this morphological study one gains the impression of vascular tubes in which there has been a marked overgrowth of swollen, spindle-shaped but otherwise mature endothelial tumor cells which have obscured the framework of the vascular tubes except when it is stained with silver carbonate and have also proliferated outside of the vascular tubes where they are associated with a rather dense meshwork of fine, tangled, reticulin fibers. One assumes that the endothelial cells have formed the reticulin fibers since no other source for them can be observed.

As already stated, this tumor differs in some respects from the other

17 hemangioendotheliomas available for study in this laboratory and some doubt was entertained regarding the interpretation of the findings upon a morphological basis alone. Fortunately, confirmatory evidence has been obtained from a study of the behavior of the explants.

TISSUE CULTURE

Method

The medium used for cultivation consisted of one part chicken plasma, three parts human placental serum and one part extract of 9 to 11 day chick embryos in a buffered saline solution. The cultures were explanted in lying-drops of the medium on coverslips according to the Maximow method, and incubated at 37° C. They were washed in buffered saline three times a week, at which time the liquid components of the medium were renewed. The saline solution used was that devised by Simms and Sanders² in 1942. The cultures were maintained in their original situation on the flying coverslip, without transfer, for as long as possible during the 4-week period of cultivation; but it became necessary to transfer most of them at least once, because of plasma liquefaction which could not be controlled by patching.

During this time different explants were fixed, at intervals, in a 4 per cent solution of formaldehyde, and in Zenker's, Helly's and Bouin's fluids. They were stained with Delafield's hematoxylin, Mallory's phosphotungstic acid hematoxylin, Weigert's hematoxylin with mucicarmine, and fuchsin-ponceau-aniline blue, or impregnated with silver by McKinney's³ modification (1929) of the Bielschowsky method, for reticulin.

Growth Characteristics

This tumor produced a sturdy, spiky growth within 24 hours. At 3 days the outgrowth had become flat and semimembranous, the cells tending to lie closely together, but not always appearing contiguous. A good many wandering cells of the macrophage type were present. At the outer boundary of the advancing sheet the cells were characterized by many needle-shaped pseudopodia pointing in a centrifugal direction (Fig. 8). The area of growth became an area of plasma liquefaction which terminated abruptly just behind this peripheral rank of cells with aiguilliform prolongations. Almost without exception the outgrowth advanced over the lower surface of the plasma clot, not through it, and lay flat against the coverslip like a membrane. Near the explant the cells tended to be elongated and slender, but toward the periphery where there was less crowding they became flatter and wider.

The outer boundaries of the cytoplasm were hardly to be discerned in the living state; consequently what appeared then, and after use of the common fixatives and stains, to be interstices between the cells may often have been areas of attenuated ectoplasm; for silver nitrate impregnation demonstrated a clear mosaic formed by the blackened cement borders of the cells (Fig. 7). After such fixatives as Bouin's, Helly's, or Zenker's fluids, all of which produce some shrinkage, there often seem to be gaps between the cells (Figs. 4 and 6). This may be an artifact of fixation, or it may be that these gaps are actually bridged by an ectoplasm too thin to be visible with the ordinary stains, as is often the case in mesothelial membranes and in capillary endothelium. The membranes formed by this tumor, however, are readily distinguishable from mesothelial membranes as we have seen them in cultures of normal and neoplastic serosae (Stout and Murray,⁴ 1942). These latter are more compact and more regular as to cell boundary. In some areas the tumor cells adopted a more fibroblast-like form, taking up positions at a more or less uniform distance from one another. The distance was in some cases so great that it was difficult to believe that these cells were contiguous.

Frequently the long axes of the cells forming a single group were oriented all in one direction. Where the outgrowth was composed of several groups, this produced the effect of streams of cells meeting, crossing, or becoming confluent (Fig. 4). Such orientation phenomena were most likely due to convection currents in the medium, which changed direction during the course of the cultivation handling (Weiss,⁵ 1934). It is interesting that such diverging and converging streams of cells simulate the conditions indicated by sections to exist in this as in many other tumors.

The cells growing out from this tumor were unusually large. (Cf. culture of fetal rat vascular endothelium photographed at same magnification, Fig. 5.) The nuclei were round to oval, containing one to four nucleoli, one and two being the most common numbers. Binucleate and sometimes multinucleate cells were seen. In the cytoplasm close to the nucleus, and often surrounding it, there were usually to be found small, uniform, moderately refractive granules which stained red supravitaly with neutral red. If the cultures were rinsed with Maximow's lithium carmine, after 2 or 3 days carmine inclusions could be seen in the cells, usually occupying a perinuclear position.

Silver staining for reticulin after a fortnight or more of cultivation demonstrated a fine but very distinct network of fibers emerging from

the explant and tapering to nothing at about half the radius of the outgrowth (Fig. 1).

DISCUSSION

Assuming that this is a primary growth in the leg, the majority of the histological possibilities for a tumor at this site could be eliminated by recourse to the sections, leaving the omnibus fibrosarcoma and neoplasms of the musculature or lining of the blood vessels as possible sources. A study of the growth characteristics of the tumor *in vitro* disposed rather readily of the first two alternatives and rather consistently supported the view arrived at independently by a consideration of the sections along with a series of other hemangioendotheliomas.

This generally membranous habit of growth, covering surfaces and forming a mosaic with cemented cell borders, does not characterize fibrosarcomas, nor any form of smooth muscle, normal or neoplastic, which is known to us. It cannot be called *typical* of vascular endothelium, but has been seen by us and reported by others in this connection. Most typically, vascular endothelium seems to grow *in vitro* in the form of solid or hollow tubes, as described, *e.g.*, by Lewis,⁶ 1931, and Scriba,⁷ 1935, in material from the embryonic chick. But Lewis⁸ also reported (1922) an epithelioid type of outgrowth (rather similar to ours) from the liver sinusoids. Others, as Silberberg,⁹ 1929, and Bisceglie,¹⁰ 1930, described outgrowing endothelial cells as taking on a form indistinguishable from that of the fibrocyte. This has sometimes occurred in our cultures and we have been inclined to regard it as one of the responses to cutting and transfer, a process which habitually interferes with differentiation in the cut region.

In cultures of a hemangioma (unpublished) we have observed both the fibrocyte outgrowth, which may have originated from connective tissue involved in the tumor, and a sheet-like proliferation composed of cells similar to those which characterize this hemangioendothelioma. And in fetal rat cultures we have observed an interesting combination of the tubular type and membranous type of endothelial habit. This occurred in explants from ribs of 20 days' gestation, at which time ossification and vascularization are proceeding *pari passu* in these bones. Figure 3 shows a network of capillaries at one end of the rib and a flat membranous outgrowth from the other. In the former the transition takes place peripherad from tubular to flat type, and in the latter, from membranous to tubular. The presence of both sinusoid and capillary endothelium in a normally developing bone makes this observation of some interest.

Under normal conditions *in vivo* or *in vitro* vascular endothelium does not stain supravitaly nor phagocytize particulate matter, as the tumor cells of our cultures did. But according to McJunkin,¹¹ 1927, the endothelium of liver sinusoids (of the adult rabbit), when properly stimulated, will do both. The sinusoids are regarded generally as a primitive type of capillary. It is not improbable that neoplastic vascular endothelium should behave similarly in some respects to embryonic or stimulated sinusoid endothelium.

Cameron and Chambers¹² reported the cultivation of a "congenital angioma . . . diagnosed as angio-endothelioma," which produced *in vitro* a variety of cells, and was characterized by the formation of "endothelial tubes." This appears to belong to a different group of vascular neoplasms from that with which we are concerned. Tubular structures which first appeared as solid cords composed of "endothelial cells" were described by Coman¹³ as developing in tissue cultures of a human "angiosarcoma" which had metastasized to a rib. Other than this no histological details were given. Consequently it is difficult to classify this tumor with exactitude.

SUMMARY

A hemangioendothelioma of unusual morphological appearance is described and its behavior *in vitro* is discussed. This particular neoplasm is regarded as manifesting itself in the form of a primitive or somewhat dedifferentiated vascular endothelium.

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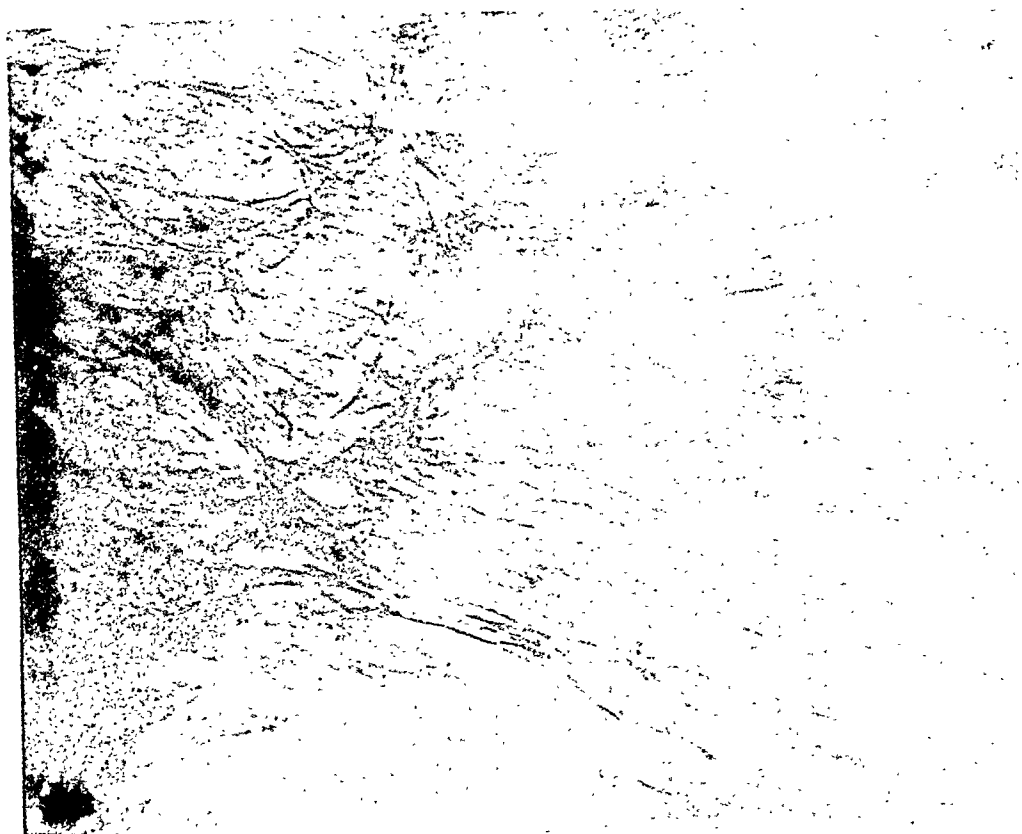
[*Illustrations follow*]

DESCRIPTION OF PLATES

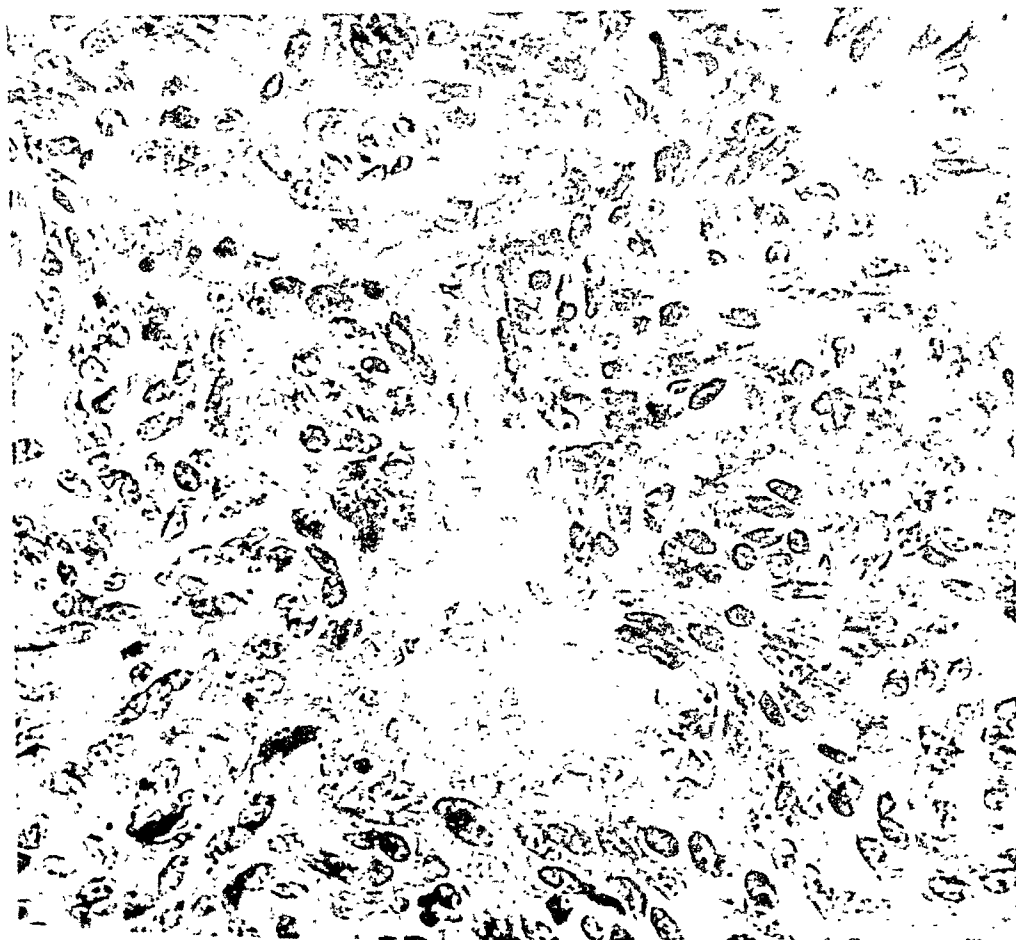
PLATE 49

- FIG. 1. Reticulin fibers formed in the midzone of tumor growth. Seventeen days *in vitro*. Formaldehyde fixation, McKinney-Foot-Bielschowsky silver impregnation. $\times 310$.
- FIG. 2. Detail photomicrograph of a section of the tumor showing a vascular space containing red blood cells lined by the spindle-shaped tumor cells. Vaguely defined cords of tumor cells pass outward from it. No normal endothelia are present. $\times 480$.

1



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Cultural Characteristics of Hemangioendothelioma

PLATE 50

FIG. 3. Six-day culture of a rib from a 20-day rat fetus, showing endothelium in capillary formation at left and in membranous habit at right. Towards the periphery the capillary cells spread out in sheet-like form. Helly's fixation, Delafield's hematoxylin stain. $\times 28$.

FIG. 4. Seventeen-day culture from the tumor, showing a stream-like pattern of cell growth. Macrophages may be seen. Bouin's fixation, Delafield's hematoxylin stain. $\times 125$.

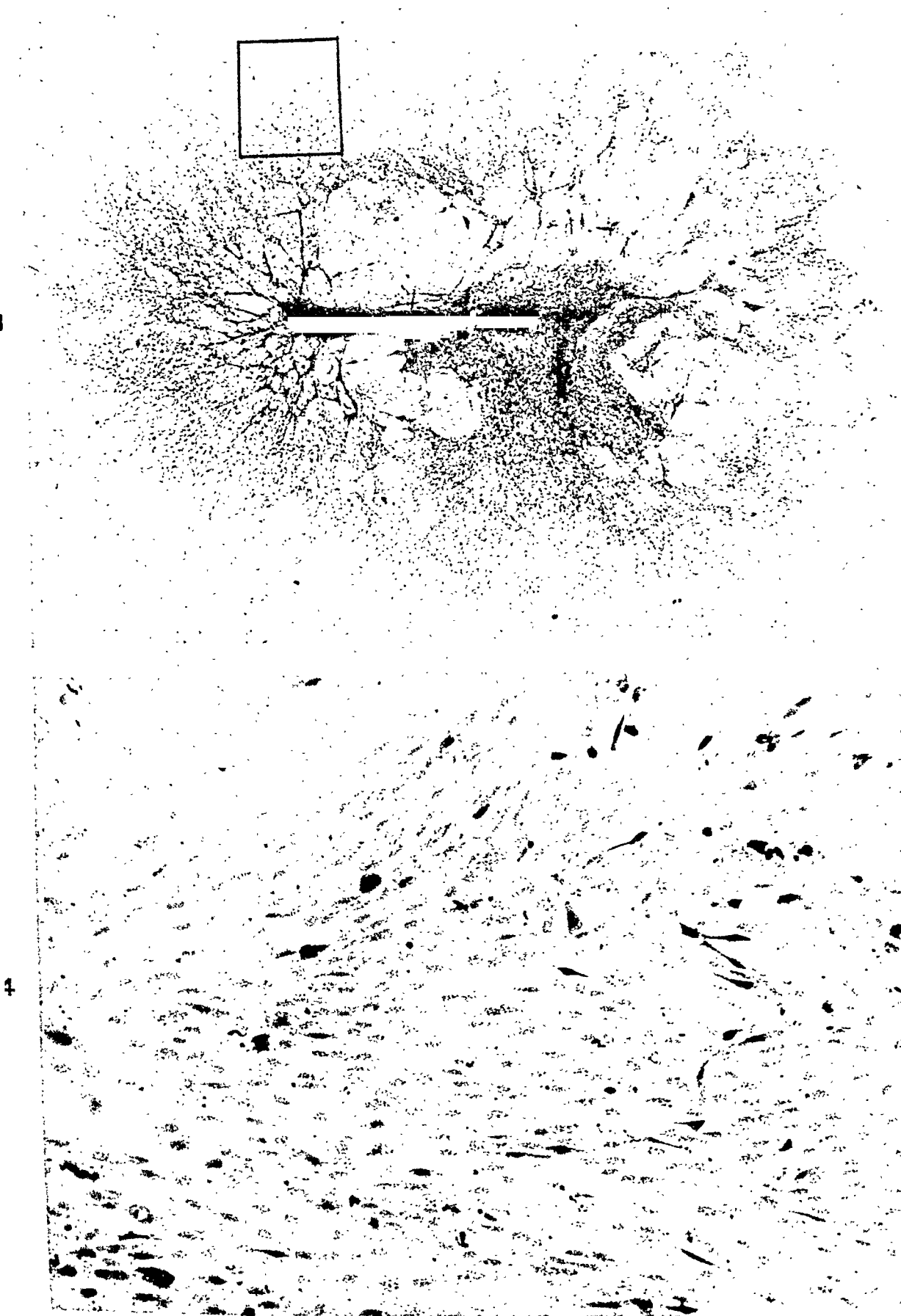
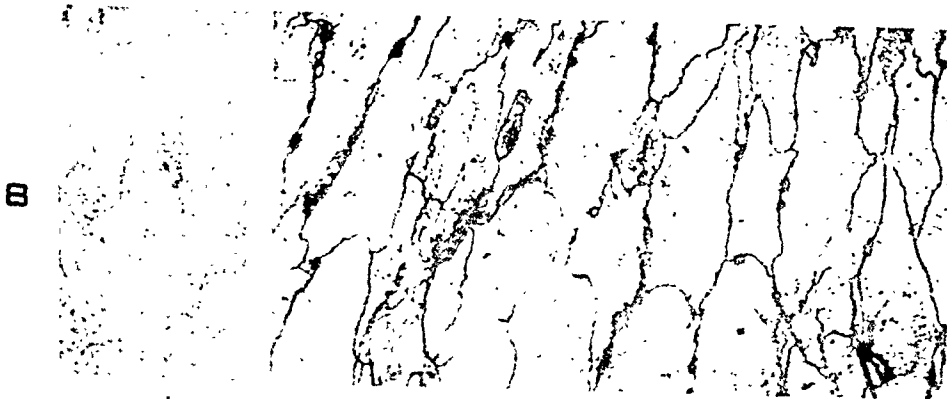
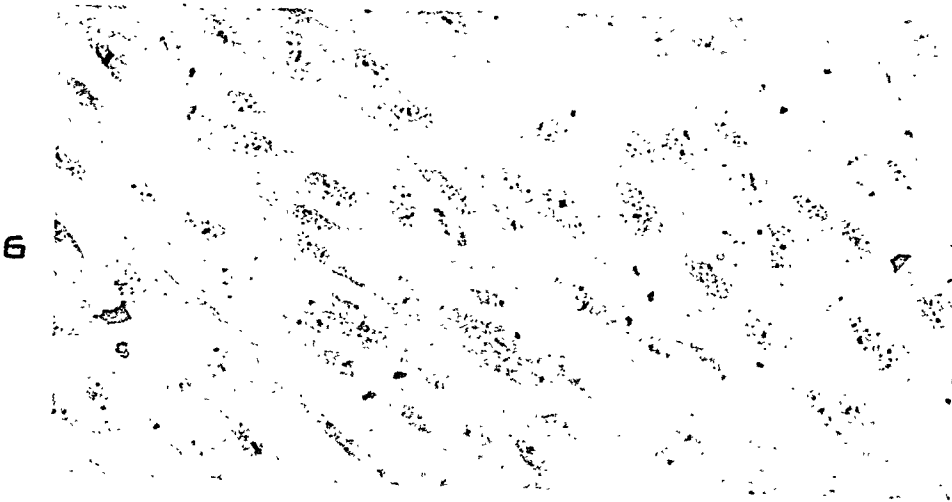
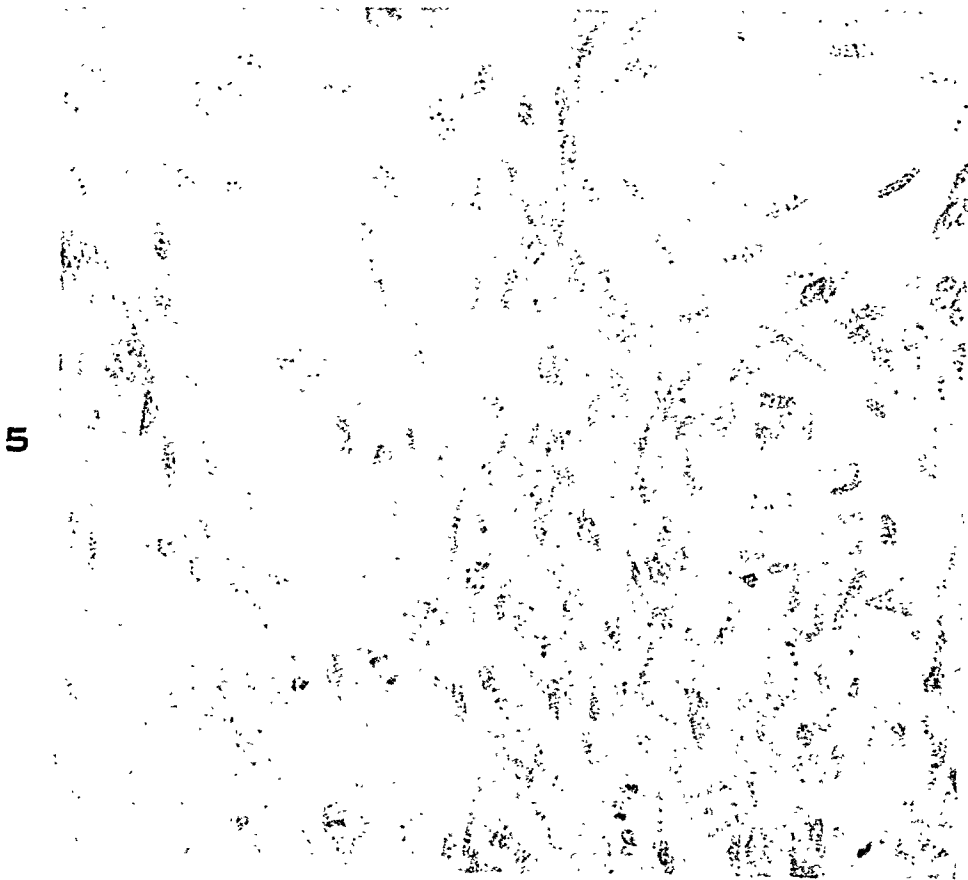


PLATE 51

- FIG. 5. Detail of peripheral sheet-like endothelial growth from the rib of the fetal rat shown in Figure 3. $\times 255$.
- FIG. 6. Detail of sheet-like growth from a culture of the tumor; 14 days *in vitro*; Helly's fixation, Delafield's hematoxylin stain. $\times 255$.
- FIG. 7. Similar growth from the tumor stained with silver nitrate to show mosaic of cemented cell borders. Fourteen days *in vitro*. $\times 255$.
- FIG. 8. Cell at periphery of 10-day culture, showing needle-shaped pseudopodia. Zenker's fixation, phosphotungstic acid hematoxylin stain. $\times 255$.



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Murray and Stout

Cultural Characteristics of Hemangioendothelioma

STUDIES ON THE DECALCIFICATION OF BONE*

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The problem of combining rapid and satisfactory decalcification and satisfactory Romanovsky staining of bone marrow remains one of difficulty. Some years back a series of experiments was made which led to our adoption of 5% formic acid in water as a decalcifying agent. This has proved quite satisfactory in routine use since 1936.

In the original study a survey was made of the effect of immersion for varying periods of time in various decalcifying agents on Romanovsky staining of rabbit marrow removed from the long bones. Periods as short as 1 day in 5% HNO_3 and 1 to 2 days in 5% SO_2 often seriously impaired marrow staining with eosin azure stains, producing a diffuse oxyphilia of nuclei as well as of cytoplasm. Treatment of marrow for 1, 2, or 3 days with our then routine decalcifying fluid: 25 cc. concentrated formic acid, 10 gm. sodium citrate, 75 cc. water; with saturated H_2SO_3 (5 to 6% SO_2), with citric acid and disodium phosphate buffer mixtures of pH 2.2, 3.0, 4.0, 5.0 and 6.0; with 6.35% NH_4NO_3 (the equivalent of 5% HNO_3), and with 14.65% NH_4Cl (the equivalent of 10% HCl) permitted excellent marrow staining after subsequent imbedding and sectioning.

Believing that injury to marrow staining might be controlled by regulation of the initial pH of the fluid, series of buffered mixtures of sulfurous and formic acids were made and pieces of rabbit bone marrow without bone were soaked in them for varying intervals, then washed, dehydrated, imbedded in paraffin, sectioned and stained by a Romanovsky method. With the H_2SO_3 -sodium citrate series, 7 days' soaking in mixtures of pH 2.75 to 5.0 still permitted excellent staining, while even 1 day at pH 1.15 to 1.30 destroyed the basophilia of nuclear chromatin. Intermediate pH levels gave intermediate effects, varying with the pH level. In this series pH levels had to be determined electrometrically. With formic acid-sodium citrate mixtures ranging from pH 1.8 to 3.15, tissues soaked for 1 week at pH 3.0 or higher still stained well, while at pH 2.0 or lower for 2 to 4 days staining was poor. At 37° C. these mixtures produced much more rapid deterioration of staining quality.

These preliminary studies indicated that a decalcifying agent which

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did not produce a pH level below about 2.0 and did not take over 4 days would be desirable.

This led us to try various buffered mixtures of formic, sulfurous and trichloroacetic acids as well as other substances for the decalcification of monkey bones fixed with dilute formaldehyde or with Orth's fluid. Among these were the ammonium salts which are known to dissolve appreciable quantities of calcium carbonate. On trial, 6.35% NH_4NO_3 solution, equivalent to 5% HNO_3 , actually dissolved 68 mg. CaCO_3 per 100 cc. in 24 hours, and 14.65% NH_4Cl , equivalent to 10% HCl , dissolved 107 mg. CaCO_3 per 100 cc. in 1 day. (The analyses were made by Senior Chemist Elias Elvove.) These two solutions partially decalcified blocks of monkey vertebra in 13 and 17 days, respectively, yielding poor sections with much remaining demonstrable calcium in bone and excellent Romanovsky staining. Both solutions had an initial pH of 5.1 and might be of value for slow decalcification of cancellous bone where avoidance of acid was important. Monkey femora were still hard after 3 weeks.

White¹ used a neutral solution of ammonium citrate (pH 6.0 to 8.0), equivalent to about 6% citric acid. He said nothing about the time required.

Similarly, 5% KH_2PO_4 with an initial pH about 5.0, gave decalcification of decorticated cancellous bone from femur and sternum in 2 to 3 days. Sections were good, hematoxylin stains did not indicate any gross amount of remaining calcium and Romanovsky staining was excellent. However, femoral shaft, knee joints and vertebrae were still hard after 18 days.

The 10% sodium citrate solution in 25% formic acid (which we were then using routinely and which is still widely used, though I do not know its source) has an initial pH of 2.35 and decalcifies monkey femora in 2 to 3 days, vertebrae in 24 to 36 hours and decorticated cancellous bone in 24 hours. Prolonging the exposure to 96 hours still permitted excellent marrow staining. Evans and Krajian² used a similar mixture of equal parts of 85% formic acid, 95% alcohol and 20% sodium citrate solution. This decalcified in 3 to 4 days and allowed good staining.

A mixture containing equal weights (27.5 gm.) of formic acid and sodium citrate, with an initial pH of 3.15, decalcified monkey vertebrae in 4 days and femora in 8 to 9 days. Subsequent marrow staining was good, and remained so with vertebrae allowed to remain for 4 additional days in the fluid.

Disodium and trisodium phosphate-formic acid mixtures with initial

pH levels of 1.8 to 2.65 decalcified monkey vertebrae in 1 to 2 days and femora in 1 to 12 days, the interval increasing with rising pH level, the quality of the sections decreasing conversely and the brilliance of Romanovsky staining satisfactory in all, but best at the highest pH level of decalcification.

Solutions containing 1 to 3% by volume of 90% formic acid (1.1 to 3.3% by weight of pure formic acid) (pH 1.9 to 2.1) decalcified rather slowly, with good subsequent marrow staining and fair cutting consistency. Those containing 4 to 25% unbuffered formic acid (pH 1.8 to 1.4) decalcified monkey vertebrae in 1 day, femora in 1½ to 3 days, with best results in about 2 days. Higher concentrations appeared to be no better than 5%, and this level gave results equal to any of the better buffered mixtures.

Similar unbuffered 1 to 25% aqueous dilutions of acetic acid (pH 2.8 to 1.9) took 2 to 4 days to decalcify monkey vertebrae, 10 to 12 days for femora, and even then sections were only fair and much calcium remained in the femoral cortex with the lower levels of acetic acid. Consistent with previous results with high pH levels in decalcification, Romanovsky staining of marrow was good with 1 to 10% acetic acid, poorer with 15 and 25% (pH 2.0 and 1.9).

Buffered mixtures of 25% acetic acid with 10 to 25% sodium citrate, with 2 to 8.3% Na_2HPO_4 and with 8 to 24% Na_3PO_4 , with pH levels ranging from 3.4 to 4.6, generally failed to soften monkey femora in 3 weeks, and only partially decalcified vertebrae in 6 to 14 days, yielding fair sections, some of which showed demonstrable lime salts, and quite variable staining.

Solutions of 80% alcohol containing 25% formic acid, 25% acetic acid or 10 or 20% salicylic acid gave no evident softening of monkey bones in 3 weeks. Similarly, Carnoy fluids containing 60 parts absolute alcohol, 30 parts chloroform and 10 parts of either 90% formic or glacial acetic acid failed to decalcify during the fixation interval.

Saturated solutions of sulfur dioxide in water (5 to 6%) decalcified decorticated cancellous bone in 7 hours, monkey vertebrae in about 15 hours and femoral shafts in about 36 hours. Sectioning was generally good and subsequent staining satisfactory. With longer exposures Romanovsky staining of marrow was impaired.

In 5% HNO_3 monkey femora, vertebrae, sterna and other bones were decalcified in 24 to 36 hours. Sections were fair to good, iron hematoxylin-picrofuchsin stains were uniformly satisfactory and Romanovsky staining gave diffuse nuclear and cytoplasmic oxyphilia.

Similarly, trial of Wilson's ³ rapid method using 20% HNO_3 *in vacuo*,

gave diffuse oxyphilia of all structures except cartilage, mucus and bone cells after only 5 hours' decalcification. Shorter intervals such as the $\frac{1}{2}$ to 3 hours claimed by Wilson for this method failed to decalcify half skulls of rats. Substitution of 25% formic acid in this procedure increased the decalcification time to 8 to 24 hours, but this time permits excellent Romanovsky staining of the surrounding soft structures as well as bone and marrow.

Since decalcification of similar bones may often be accomplished in 24 hours with 25% formic acid, it is questionable whether Wilson's³ preliminary defatting procedure has any great influence. Comparative tests made by immersing similar bones in the same formic acid solution *in vacuo* and in air showed no difference in the length of time required for decalcification.

DeGalantha's⁴ complicated HNO_3 , alcohol, picric acid, olive oil formula claims no quicker or better decalcification than we have obtained with 5% formic acid, and his statement about subsequent staining does not cover the sensitive Romanovsky methods.

Monkey vertebrae and femora were decalcified in 24 hours in 5% trichloroacetic acid, sections were good and subsequent iron hematoxylin-picrofuchsin and Romanovsky stains were satisfactory. However, on account of the high molecular weight (163) a larger amount is required to avoid exhaustion than with formic acid (mol. wt. 46) or sulfurous acid ($\frac{1}{2}$ mol. wt. = 41), and the present (1943) cost of trichloroacetic acid is four times that of formic acid.

Since 5% formic acid was as efficient a decalcifying agent as any of those tried which did not also seriously impair Romanovsky staining of bone marrow in a short time, two series of decalcification of weighed samples of shaft of monkey femur and tibia were made with varying proportions of 5% formic acid, to determine the necessary quantity for prompt decalcification. In the first series bones were removed as soon as apparently decalcified, in about 2 days, washed and weighed, then dehydrated, sectioned in paraffin and stained with iron hematoxylin-picrofuchsin and with the buffered Romanovsky stain. In the second series the blocks were left in the same decalcifying fluid for twice the time necessary for apparent decalcification, then washed, weighed and treated as before. Blocks treated for 2 days with 10 to 30 cc. of 5% formic acid per gram lost an average of 25% of their weight; those treated with 40 to 100 cc. lost 33%. Those treated for 4 days with 10 to 30 cc. per gram lost 31%; those with 40 to 100 cc., 32%. All sectioned well and Romanovsky and van Gieson connective tissue stains were satisfactory.

Substitution of 5 cc. of 90% formic acid for the usual 5 cc. of glacial acetic acid in Zenker's fluid gives at least partial decalcification in 24 hours, much better even than the 10 cc. glacial acetic acid often recommended for this purpose, and the usual picture of Zenker's fixation seems little altered. Likewise, inclusion of 5% formic acid in Bouin's fluid in place of the usual acetic acid makes it a quite efficient decalcifying agent. Similarly the "PFF" fluid recently reported from this laboratory,⁵ which contains 5% formic acid, and 10% strong Formalin (4% formaldehyde), saturated with picric acid, decalcifies small bones well in 1 to 2 days.

The fluid of McNamara, Murphy and Gore⁶ (HgCl_2 , 10; trichloroacetic acid, 30; concentrated HNO_3 , 5; strong Formalin, 40; 95% alcohol, 50; water, 400) is said to require 3 to 5 days for decalcification, and to impair nuclear staining in over 7 days. They do not note its effect on Romanovsky staining.

CONCLUSIONS

Slow decalcification of decorticated cancellous bone with excellent subsequent marrow staining by Romanovsky stains may be accomplished with ammonium nitrate, ammonium chloride, or potassium acid phosphate, but decalcification of cortical bone is too slow for practical use.

Buffered sodium citrate formic acid mixtures with initial pH above 3.0 are a little faster, decalcify cortical bone slowly and permit good marrow staining even with several days' exposure beyond apparent decalcification.

Buffered formic acid solutions with initial pH around 2.5 are faster, but show more tendency to impair marrow staining and are generally no better in either respect than 5% aqueous formic acid, which apparently is as good as higher concentrations of the same acid.

Acetic acid is a relatively inefficient decalcifying agent, and appears to show somewhat less margin of safety between adequate decalcification and impairment of chromatin staining.

Trichloroacetic acid is a good decalcifying agent, but more is required, and the cost is higher than for formic acid.

Nitric and sulfurous acids are prompt decalcifying agents, but the first as promptly spoils Romanovsky staining of marrow, and the second tends to do so if decalcification takes 2 days or more.

With 5% formic acid, 40 cc. per gm. of bone should be used for prompt decalcification.

For simultaneous fixation and decalcification, addition of 5 per cent

formic acid in place of acetic can be recommended in such fluids as Zenker's, Bouin's and "PFF."

Eighty per cent alcohol solutions of formic, acetic and salicylic acids do not decalcify, nor do acetic or formic Carnoy's fluids.

The use of vacuum during decalcification is of no particular advantage except to remove bubbles in large specimens, and preliminary defatting apparently saves little time in the decalcifying fluid.

I have referred freely to the various manuals on histologic technic (Mallory's,⁷ Lee's,⁸ Schmorl's,⁹ Romeis',¹⁰ Langeron's¹¹) but have attempted no complete review of the literature.

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TOOTH BUDS AND JAWS IN PATIENTS WITH CONGENITAL SYPHILIS CORRELATION BETWEEN DISTRIBUTION OF *TREPONEMA PALLIDUM* AND TISSUE REACTION*

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INTRODUCTION

Shortly after the discovery of *Treponema pallidum* many attempts were made to demonstrate it in the bones of stillborn and living-born congenitally syphilitic infants. However, these early efforts failed due to the imperfect histologic methods of that time. It was not until Levaditi¹ (1905) and Bertarelli and Volpino² (1906) introduced their staining methods that *T. pallidum* was occasionally demonstrated in sections of a single bone of congenitally syphilitic fetuses or infants. The first, and as yet not repeated, systematic study on the distribution of *T. pallidum* in all bones of congenitally syphilitic stillborn and living-born infants was conducted by Schneider.³ He must be given credit for having proved definitely that the various bone changes in congenital syphilis, such as osteochondritis, periostitis and osteomyelitis, are but localized tissue reactions to the invasion of *T. pallidum* and to the toxins of broken-down spirochetes.† Schneider's study showed that bone is the favorite site for the spirochetes, which lodge and multiply tremendously, particularly in those parts of the bone wherein very active growth is going on. The reaction to the appearance of the organism in these areas of bone is a very definite inflammation of the osteogenetic tissue resulting in an interference with normal osteoblastic action.

With the spread of *T. pallidum* throughout the whole skeleton in congenital syphilis, the organism was expected to be found in the jaws and also within the tooth buds. However, the lack of adequate material and the difficulty of staining spirochetes in bone sections led to the advancement of the theory that the enamel lesions of the well known Hutchinson's teeth result from a syphilitic disturbance of endocrine glands, specifically the parathyroid glands. This theory, brought forward particularly by Kranz,⁴ found as many supporters as the theory that a superimposed rickets is the cause of Hutchinson's teeth. These concepts were not abandoned or were not even considered doubtful

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† Throughout this article "spirochete" refers to *Treponema pallidum*.

when Cavallaro,⁵ Pasini⁶ and Del Guasta⁷ occasionally succeeded in showing spirochetes only in the vessel walls of some tooth buds. These authors limited their studies to the proof of the presence of *T. pallidum* in a small area, for instance in the pulp, but did not deal with the tissue changes and certainly not with the correlation of tissue changes with spirochetosis.

In this country the first attempt to demonstrate *T. pallidum* in the tooth buds of syphilitic fetuses and to correlate the reaction of the tissue with the Hutchinson's deformities was made by Hill.⁸ Hill was correct in stating that the "hypoplasia of the enamel cannot be explained as the result of spirochetosis unless the organisms can be found intimately associated with the areas of degeneration." However, he was not able to prove the presence of spirochetes in the "dental anlage" of nine suspected congenital syphilitic fetuses using the staining techniques of Levaditi, Warthin-Starry, Jahnelt and Giemsa. Therefore, Hill concluded "that there is insufficient evidence to justify the conclusion that the characteristic congenital syphilitic dental deformities are the direct result of the invasion of the enamel organ by the *Treponema pallidum*."

Simultaneously with Hill's⁸ article, I⁹ published in 1931 the results of microscopic studies of four congenitally syphilitic fetuses and infants. I demonstrated not only the presence of innumerable *T. pallidum* in the pulp, the dentinoid, the dentinal tubules, the tooth sac, the ameloblast layer and even in the stellate reticulum, but I was also able to demonstrate the reaction of the tissue to the spirochetosis by dividing the jaws in midline, using one-half for the spirochete demonstration while the other half served for tissue studies. The correlation between the presence of innumerable spirochetes and the inflammatory reaction on the part of the tissue, resulting in degenerative changes of the ameloblasts and odontoblasts, became evident. The tooth buds so involved were those of both the deciduous and the permanent teeth.

My conclusions that the characteristic lesions of the Hutchinson's teeth are due to the syphilitic inflammation within and around the tooth buds were fully confirmed by Pflüger,¹⁰ who studied the jaws of nine syphilitic infants microscopically but did not attempt to demonstrate the organism in the tissue.

Boyle,¹¹ in his histologic findings in the tooth buds of syphilitic fetuses, stressed the presence of inflammatory changes and their results. However, he particularly emphasized the defective calcification of the dentin as represented by numerous interglobular spaces and extremely

wide zones of predentin. Boyle made no reference to the presence of the spirochetes.

Burket¹² examined the jaws of two congenitally syphilitic infants, one 4 and the other 8½ months of age, both of whom received anti-syphilitic treatment. He was unable to show the organism in the dental tissue. Nevertheless, he concluded that the localized changes which he described, "such as the enamel hypoplasias, metaplasia or aplasia of the ameloblasts, could conceivably be produced by the local activity of the *Treponema pallidum*." According to Burket, the changes of the buds of the permanent teeth were confined to the enamel organ while those of the buds of the deciduous teeth were evident only in the dentin and pulp.

Since the authors of even the recent editions of textbooks of oral pathology have been reluctant to accept my conclusions as to the pathogenesis of Hutchinson's teeth and are inclined to adopt the endocrine origin, I have made further studies on the jaws of six congenitally syphilitic but nonmacerated subjects: four fetuses of 6, 8, and 9 months and two infants of 2½ weeks and 1½ months of age.

Two of the fetuses exhibited radiographically and microscopically an osteochondritis syphilitica and periostitis syphilitica (Fig. 1), while the other two fetuses and the infants revealed only a periostitis syphilitica of the long bones and the jaws.

This sequel to my previous investigations is concerned with the following main questions:

1. Can *T. pallidum* be demonstrated in the tooth buds and jaws of congenitally syphilitic fetuses and infants?
2. Can the lesions of these organs in congenital syphilis be related to an endocrine disturbance of calcium and phosphorus metabolism?
3. Are the tooth buds of both dentitions involved and does the involvement always evolve symmetrical lesions?

STAINING METHOD

The jaws were divided in the midline and most of the long bones and some ribs and the clavulae were cut in half in their long axis, thus providing equal parts of the same bone for the spirochete stain and for the routine hematoxylin and eosin stain.

The silver impregnation after Bertarelli and Volpino,² a modified Levaditi method, proved to be the technic of choice to demonstrate the *T. pallidum* in celloidin or paraffin sections of about 5 to 6 μ thickness. The specimens, carefully and thoroughly decalcified in 5 per cent nitric

acid, were divided into small blocks, neutralized, washed and placed in the silver solution at 37° C. for 18 days, according to the method which follows. Decalcification does not hamper the staining of the *T. pallidum*. Bertarelli and Volpino's technic offers the great advantage that the sections, in which the spirochetes stain black, can be counterstained by hematoxylin and eosin, thus enabling the investigator to study simultaneously the distribution of the organisms and the tissue reaction.

Method for demonstrating *T. pallidum* in bone:

Precautions

1. Absolute cleanliness.
2. Bottles should be dark amber.
3. Solutions must be prepared immediately before use.

Technic

1. Fix in a 2% solution of formaldehyde or in alcohol. Alcohol fixation requires a longer time.
2. Decalcify very thoroughly in large quantities of 5% nitric acid.
3. Cut the bones into blocks 5 to 10 mm. thick.
4. Place the blocks in 5% sodium sulphate for 2 days.
5. Wash in tap water for 2 days.
6. Place in the following solution, freshly prepared:

Silver nitrate—1.5 gm.

Water, distilled—50 cc.

96% alcohol—50 cc.

Glacial acetic acid—4 to 5 drops

This silver impregnation must be carried out in complete darkness at 37° C. for about 18 days. Change the solution when it becomes cloudy.

7. Wash in distilled water for 1 day, changing frequently.

8. Place in the following solution for 48 hours in darkness at room temperature:

Tannic acid—3.0 gm.

Gallic acid—5.0 gm.

Sodium acetate—10.0 gm.

Water, distilled—350 cc.

Change solution when it becomes cloudy.

9. Wash carefully in distilled water, changing several times a day.
10. Place successively in 70%, 80%, 95% and absolute alcohol.
11. Embed in paraffin or celloidin. If paraffin is used, interpose cedar-oil between xylol and paraffin.
12. Cut sections 5 μ in thickness. The treponemes are black; the tissue appears yellow. The sections may be counterstained with hematoxylin and eosin.

DISTRIBUTION OF *T. PALLIDUM* IN THE TOOTH SAC AND THE ENAMEL EPITHELIUM

The structure of the spirochetes seen in the bone and tooth tissues varied from the typical long, spiral type to various degenerative forms. The organisms in most of the fetuses constantly appeared tightly twisted with pointed ends and with regular spirals of regular amplitude

and depth. The organisms in stillborn or livingborn infants, however, occasionally showed regressive changes as to size and shape. Their ends were thickened and rounded, the number of the spirals markedly reduced; some were partially straight, their bodies appearing granular and finally breaking into many pieces. The older the infant the fewer were the spirochetes. The results of my study of the distribution of the *T. pallidum* in the skeleton showed that the tooth sacs of the tooth buds of the deciduous teeth and those of the permanent teeth harbor a greater amount of organisms than any other tissue of the osseous system. Moreover, even if the spirochetosis gradually disappeared, as was seen mostly in syphilitic infants, and if the periosteum and even the primary bone marrow next to the epiphysis contained scarcely any organisms, there were masses of them demonstrable in the tooth sac of the buds of the deciduous and permanent teeth.

This fact might be explained as being in accordance with Schneider's³ observation of a striking accumulation and persistence of *T. pallidum* in bony areas of pronounced growth activity, which I was able to confirm. They were more persistent there than in the pulp. It is obvious that the extreme vascularity of the tooth sac tissue adjacent to the enamel epithelium and the Hertwig's sheath played an important rôle in the spread of the organisms. It is the blood stream that carried them into the tissue. The organisms penetrated through the blood vessel walls and moved into the tissue where they multiplied. There were innumerable spirochetes in the tooth sac layer next to the enamel epithelium (Fig. 2). They formed braid-like masses of twisted organisms which were brought there by the dense network of capillaries that intruded the outer epithelial layer (Fig. 3). It did not make any difference whether the outer epithelial layer still outlined the stellate reticulum or already covered the stratum intermedium as a constituent of the united epithelium.

While the spirochetes lay interspersed between the fibrous tissue of the alveolar and intermedial layer of the tooth sac, arranged in stripes, they formed dense whorls within the destroyed enamel epithelium. Yet relatively few of them penetrated into the ameloblast layer between the cells. Here they rested parallel to the ameloblasts, while others, having advanced farther, lay between the ameloblasts and the enamel surface and parallel to the latter. A similar spread occurred in the region of the Hertwig's sheath where numerous organisms were observed both outside and inside this epithelial loop. The organisms were noticed also in the tooth sac of the tooth buds of the first permanent molars.

The stellate reticulum, fully preserved, contained only a very few

spirochetes scattered here and there, which might be due either to its avascularity or to the protection by the outer epithelial layer. Indeed, the continuous enamel epithelium seems to be a barrier against the invasion of *T. pallidum* and must be destroyed at least partially to pave the way for their advance.

DISTRIBUTION OF *T. PALLIDUM* IN PULP AND DENTIN

On the whole the organisms were less numerous in the pulps of the tooth buds of the deciduous teeth and the first permanent molars than in the dental sacs. They were observed in the basal part rather than in the coronal area of the pulp, and there particularly in the region around and between the odontoblasts. They were transmitted to this area by the dense loops forming the capillaries of the pulp. While quite a few spirochetes appeared embedded in the predentin, some of them penetrated further into dentinal tubules. This is possible, since the thickness of the dentinal tubules varies from $1.3\ \mu$ to $4.5\ \mu$ while the average thickness of *T. pallidum* does not exceed $0.25\ \mu$ (Fig. 4).

Wherever Hertwig's sheath intervened between pulp and tooth sac the organisms in the pulp tissue were less abundant than in the adjacent sac. Here again one leans to the idea that it might have been this epithelial layer that prevented the organisms lying in the tooth sac from invading the pulp through the intact Hertwig's sheath.

DISTRIBUTION OF *T. PALLIDUM* IN THE JAW

The distribution of organisms throughout the jaws was not uniform. There was a striking difference between the abundant spirochetes in the tooth sac and the relatively small amount of organisms in the bone. While the bone marrow next to the tooth buds still contained a fair number of spirochetes, they decreased rapidly toward the outer areas but increased again in the new periosteal bone layer and in the periosteum. However, nowhere within these bones did the organisms appear in such dense masses as within the tooth bud. Many of them showed degeneration such as shortening and breaking up into small fragments or even into granules, whereas those around and within the tooth bud were very well preserved.

The spirochetes in the bone marrow were mostly concentrated around the capillaries and occasionally around the osteoblasts. Such osteoblasts, together with the organisms, had been included within the bone substance. This may explain the finding of bone cells, the lacunae of which were filled with spirochetes. Of course, such osteocytes notably were observed within the newly formed bone trabeculae of

periosteal and endosteal origin, in areas of extensive inflammatory reaction (Fig. 5). Schneider,³ who was the first to describe *T. pallidum* in osteocytes, advanced the idea that these organisms might be freed in the course of bone resorption later on, thus making a recurrence possible. Particles of broken-down spirochetes were found within leukocytes in the bone marrow. The periosteum of the jaws contained abundant organisms, mainly perivascularly arranged and better preserved than those in the bone marrow.

TISSUE CHANGES

In the cases of congenital syphilis which I studied, I noted that the intensity of the tissue changes increased proportionally with the degree of degeneration of the spirochetes. Areas containing abundant, well preserved organisms showed minor tissue alteration. This observation agrees with the concept of Schneider,³ who developed the idea from his studies that it is particularly the breaking down of the spirochetes that produces the tissue reaction. Of course, a different conclusion might be drawn from this observation: it might be the case that the inflammatory reaction gradually destroyed the spirochetes.

The tissue reaction varied with the age of the child: syphilitic fetuses showed less reaction than syphilitic infants. This might be explained by the still moderate capability of the fetal tissue to produce reactive changes to the invasion of the organisms, except in areas that harbor an extreme number of them. The tissue of an infant, however, more readily responds with inflammatory changes to the same irritation.

Changes of the Tooth Sac and the Epithelial Tissue of the Tooth Buds

The authors who studied the congenital syphilitic changes of the tooth buds overlooked the reaction of the tooth sac tissue, though it deserves the greatest attention. It is the mesenchymal structure that first and to the most striking degree undergoes changes due to the toxic effect of *T. pallidum*. The starting point of this involvement was the inflammatory reaction around the small, most frequently dilated, but sometimes obliterated vessels (obliterative endarteritis). The walls and the tissue about these vessels contained abundant spirochetes as was previously described. This cellular infiltration was composed of relatively few leukocytes, chiefly lymphocytes, and a startling number of plasma cells (Fig. 6). Dense layers of wavy fibrous tissue, interspersed with masses of collagen, were accumulated around the vessels. Extremely conspicuous strands of collagen, intensively stained with eosin, contrasted with the plasma cells and the other cells of chronic

inflammation which were scattered over the whole tooth sac. These changes occurred mainly in the layers of the tooth sac adjoining the tooth bud and the bony crypt. The islands of collagen adjacent to the bony crypt formed the matrix of atypical and primitive bone formation which was either in connection with the trabeculae proper of the bony crypt or free in the tooth sac (Fig. 7). Deeply blue-stained, irregularly calcified strands formed a latticework within the collagen, thus encircling and gradually replacing it. Connective tissue cells were embedded within these strands. This abortive bone was not produced by osteoblasts but was formed by infiltration of calcium salts into collagen and the surrounding connective tissue.

There were occasional large areas of exudate scattered throughout the fibrous tissue. They mainly occupied the region next to the tooth buds (Fig. 8).

All of the constituents of the enamel organ revealed changes. The tooth buds of the deciduous teeth were found to be more affected than those of the permanent teeth. The enamel epithelium showed alterations ranging from hydropic degeneration to partial or complete destruction, according to the intensity of the reaction in the tooth sac. Occasionally a small-cell infiltration was observed in this layer. Large masses of exudate intervened between enamel and enamel epithelium, detaching and destroying it in some areas (Fig 9).

The stellate reticulum, in which only a few spirochetes were seen, sometimes manifested no changes at all although other tissues of the tooth bud were extremely altered. However, occasionally degeneration or a stunted development was observed. The long processes connecting the cells with each other appeared thicker, or the cells had lost their stellate appearance, or the stellate reticulum was replaced by a fibrous reticulum which contained only a few cells or none at all. Sometimes the whole stellate reticulum disintegrated and only remnants of it were left.

Even though the stratum intermedium appeared to be somewhat hyperplastic or normal, the ameloblasts manifested striking alterations. There was a decrease in size of the ameloblasts. They either took up the appearance of common squamous epithelial cells or their arrangement became disturbed and at the same time they became elongated and bent. Here and there the continuity of the ameloblastic layer was broken up into small islands and edematous connective tissue of the tooth sac became adjacent to the enamel (Fig. 9). The most prominent changes, however, were noted in the cytoplasm of the ameloblasts. They showed hydropic degeneration which led to swelling and rupture

of the granular cytoplasm. Occasionally, the ameloblastic layer became detached from the enamel by exudate.

Hertwig's epithelial sheath in some instances was also markedly altered by degeneration. Its cells were either converted into a mass of cell debris or its affected layers appeared separated by exudate containing remnants of epithelial cells.

As to the changes of the enamel, two types of involvement stood out: there were globular depositions of abortive enamel between the normal enamel and the more or less affected ameloblasts (Fig. 10); or, there was only a thin layer of normal enamel without any coat of ameloblasts. The first was the imperfect product of damaged ameloblasts while the latter feature was brought about by a more rapid destruction of the ameloblasts, so that enamel formation became stunted.

Changes in the Dentin and the Pulp

It is important to emphasize that no disturbances of calcification of the dentin were observed. The thickness of predentin did not exceed the normal limit and its border toward the calcified dentin was sharp and even. The predentin did not contain any vessel or cell inclusions.

Changes in the pulps and dental papillae were not nearly so pronounced as they were in the other connective tissue structures and were observed only in infants. The vessels were dilated and surrounded by a moderate small-cell infiltration. A few hemorrhages were scattered through the pulps, the tissue of which was converted into fibrous tissue with pulp cells that had lost their protoplasmic processes.

Generally, the alterations of the odontoblasts were not such as would have been expected. These cells seemed to function quite satisfactorily despite the irregularity of their arrangement and the changes in their size. Occasionally, small areas of them had disappeared due to degeneration so that fibrous pulp tissue bordered the predentin.

There was one case, an infant, 2½ weeks old, with a very remarkable pulp involvement. The pulps of the upper central deciduous incisors were converted into granulation tissue extremely rich in round cells, interspersed with a few small, necrotic areas. No odontoblasts were found next to the exceedingly narrow predentin layer; however, there were fairly sharply circumscribed areas of dense small-cell infiltration, the plane contour of which was adjacent to the dentin while the convex contour expanded into the pulp and was surrounded by a fibrous layer (Fig. 11). Spotty areas of necrosis were found inside and outside these lesions which were located in the region of the rich vascular plexus about and between the odontoblasts. Although spirochetes

were not observed in these sections, probably because they were destroyed by the extreme tissue reaction, the tissue changes must be related to congenital syphilis. I am inclined to believe that prior to the tissue reaction these areas of massed capillaries were surrounded by dense clumps of organisms which subsequently were destroyed by a dense infiltration of leukocytes.

These roundish granulomas resembled the structures that were described as "miliary syphilomata" and were found by Herxheimer¹³ in the liver, adrenals, lungs, spleen and bones of patients with congenital syphilis. The "miliary syphiloma," a term that is not an appropriate one, must not be confused with the specific gumma.

Changes in the Jaw

The bone marrow was converted into a fibrous-edematous tissue containing dilated vessels surrounded by an inflammatory infiltration consisting largely of plasma cells. Some vessels showed an endarteritis. The bone marrow of the peripheral parts of the bone consisted of a very dense fibrous tissue. Strands of collagen and cells were included in the calcification and formed the matrix of a sort of "bone" that developed without osteoblastic activity. This type of heavily calcified trabeculae was also laid down on the walls of the mandibular canal, thus encroaching upon it (Fig. 12). These calcified structures were abundantly developed and some of them formed the basis upon which normal bone was deposited by osteoblasts. Osteoclastic activity was almost negligible. Periosteal osteophytes, the product of syphilitic periostitis, made up a thick layer that consisted of the kind of "bone" previously described. They were in connection with the old bone or separated from it by granulation tissue rich in collagen and small-cell infiltrations.

The periosteum revealed chronic inflammation.

THE NATURE OF THE LESIONS DESCRIBED

Since the material of the present study was obtained from fetuses and infants of very early age, any thought that rickets might have produced the lesions must be excluded. Moreover, there was no microscopic evidence whatsoever of tissue changes that could be related to a systemic disturbance of calcium and phosphorus metabolism. While it is true that the changes of the ameloblasts and the results thereof resembled those seen in disturbances of calcium metabolism, the dentin and the bones in patients with congenital syphilis did not show any of the alterations that are so significant and peculiar to disturbances of calcium metabolism. There were no extremely wide zones of dentinoid or

osteoid, no irregular globular calcification of the dentin, no capillaries enclosed within the dentinoid such as I have described pertaining to human and experimental rickets and to any other severe illness that interferes with the normal calcification of the tooth bud and the bone. On the contrary, the calcification of the dentin and of the bones of the material studied must even be considered as excessive. However, more important is the fact that I have proved the presence of abundant spirochetes and of a reactive chronic perivascular inflammation composed mainly of plasma cells and lymphocytes, associated with a fibrosis and a production of collagen, the predominant feature of syphilitic inflammation.

The occurrence of periostitis or osteochondritis syphilitica, or both, in all of my cases—roentgenologically and microscopically observed—added further support to my concept that all changes in the jaws are syphilitic. No specific rachitic changes could be seen in sections of the long and flat bones. Furthermore, it is significant that the syphilitic lesions which I studied did not involve symmetrical groups of teeth of the same developmental period as is characteristic of systemic disturbances of calcium and phosphorus metabolism. The morphologic changes were noted also in single teeth.

In the alleged association of a systemic disturbance of calcium and phosphorus metabolism with the morphologic changes in congenital syphilis, one should expect changes in the parathyroid glands. However, Schneider³ was unable to find alterations of these glands although spirochetes were very numerous in them.

The fact that congenital syphilis might be complicated with rickets or with some other disturbance of calcium-phosphorus metabolism must be admitted. In fact, scrutiny of the few cases employed by some authors for the study of the tooth bud changes in congenital syphilis convincingly showed alterations pathognomonic of rickets (in children above 3 months of age) or of disturbances of calcium metabolism of other origin (in fetuses or in younger children). Case no. 10 in Pflüger's¹⁰ report belongs to this group and combines congenital syphilitic and rachitic lesions.

Boyle's¹¹ observation of a striking disturbance of dentinal calcification with broad predentin layers cannot be directly attributed to syphilitic action for the reasons mentioned.

Some of the cases microscopically examined showed syphilitic inflammation affecting tooth buds, of both the deciduous and the permanent dentition. It was due to the age of the cases studied that the lesions were more pronounced in the further developed buds of decidu-

ous teeth than in those of the first permanent molars, although there was no marked difference in the number of spirochetes about or within the organs of the two dentitions.

The inflammatory involvement of the odontoblasts and the ameloblasts of the buds of the first permanent molars was still slight because of their early developmental phase, yet there was a distortion of the shape of these buds. This disfiguration was brought about by the pressure of the extremely dense fibrous granulation tissue of the tooth sac. This observation explains fully the clinical conclusions of Sarnat, Schour, Shaw and Heupel¹⁴ that "In congenital syphilis the teeth may show disturbances in the development phases which occur during the neonatal and earliest infancy periods. At this time the deciduous teeth are active in enamel formation (apposition) and may therefore show hypoplasia (chronologic enamel aplasia); while the permanent teeth which are active in morpho-differentiation may show a disturbed dentino-enamel junction with a resulting characteristic distortion of the crown (Hutchinson incisor, Moon molar)."

SUMMARY

In disagreement with the results of some investigators, this study proved the presence of abundant spirochetes in the jaws and tooth buds of both dentitions in fetuses and infants with congenital syphilis. They were demonstrated in braid-like masses of twisted spirochetes in the highly vascular tooth sac, particularly next to the outer epithelial layer. They had migrated through the stratum intermedium into the ameloblastic layer and were also found in the avascular stellate reticulum. They were brought by the vessels into the dental papillae and pulps and then multiplied noticeably about the odontoblasts. They were seen in the predentin and within the dentinal tubules of the well calcified dentin.

The excessive number of spirochetes about and within the tooth buds must be attributed to the well known fact that the greater intensity of invasion of spirochetes is reached in areas of more intensive growth activity.

The nests of spirochetes within the osteocytes of bone trabeculae might help to explain syphilitic recrudescence. The bone marrow, and particularly the periosteum, harbored many organisms. In infants many spirochetes have undergone degenerative changes or have disintegrated.

The reaction of the tissue to the invasion of *T. pallidum* in congenital syphilis lagged behind the appearance of masses of spirochetes about

and within the tooth buds and became particularly evident after birth. Referring to the inability of the early fetal organism to defend itself, Ekehorn¹⁵ said rightly that the spirochetes of syphilis do not need much energy for self defense; all they have to do is to nourish themselves, to multiply and to spread. However, towards the end of intra-uterine life, particularly in postnatal life, the response of the tissues to the organisms became evident and reached its climax when they had degenerated. The reaction was seen in the tissues about and within the tooth buds, in the marrow and the periosteum of the jaws. All these tissues demonstrated a productive syphilitic inflammation about the vessels with a distinctive number of plasma cells and lymphocytes and a few large mononuclear cells. The tooth sacs especially were turned into a dense fibrous tissue with plasma cells and lymphocytes, occasionally showing accumulations of polymorphonuclear cells and other exudate. A very marked fibrosis with patchy masses of collagen was usually seen in them. Subsequently, degenerative changes were observed in the enamel epithelium, here and there leading to the complete destruction of the ameloblasts. As a result, formation of abortive enamel and also cessation of enamel production occurred.

The pulps were converted into fairly dense fibrous tissue with a moderate perivascular infiltration and their odontoblasts degenerated less frequently and to a far less degree than the ameloblasts. In one case the odontoblasts had disappeared and circumscribed areas of round cells with spotty necrosis, surrounded by fibrous tissue, were observed in the pulp.

None of the cases studied revealed any systemic disturbance of the calcification of the dentin and bone. The dentinoid and osteoid zones were of normal thickness. The broad layer of periosteal bone was the result of syphilitic periostitis. The new bone trabeculae, developed within the dental sac, were formed by an excessive yet irregular calcification of collagenous tissue.

It is the chronic, extremely productive syphilitic inflammation of the tooth sac that damages or destroys the ameloblasts; thus producing enamel hypoplasia. It is also this inflammatory reaction in the tooth sac that exerts pressure upon the early tooth bud and brings about the alteration of its shape.

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DESCRIPTION OF PLATES

PLATE 52

- FIG. 1. Radiographs of the tibia and fibula of a stillborn syphilitic infant showing periostitis and moderate osteochondritis.
- FIG. 2. Spirochetes (*Treponema pallidum*) in the reduced enamel epithelium and the tooth sac of a stillborn syphilitic infant. $\times 1300$.
- FIG. 3. Spirochetes surrounding the vessels of the outer enamel epithelium. $\times 1300$.

1



2



3

Bauer

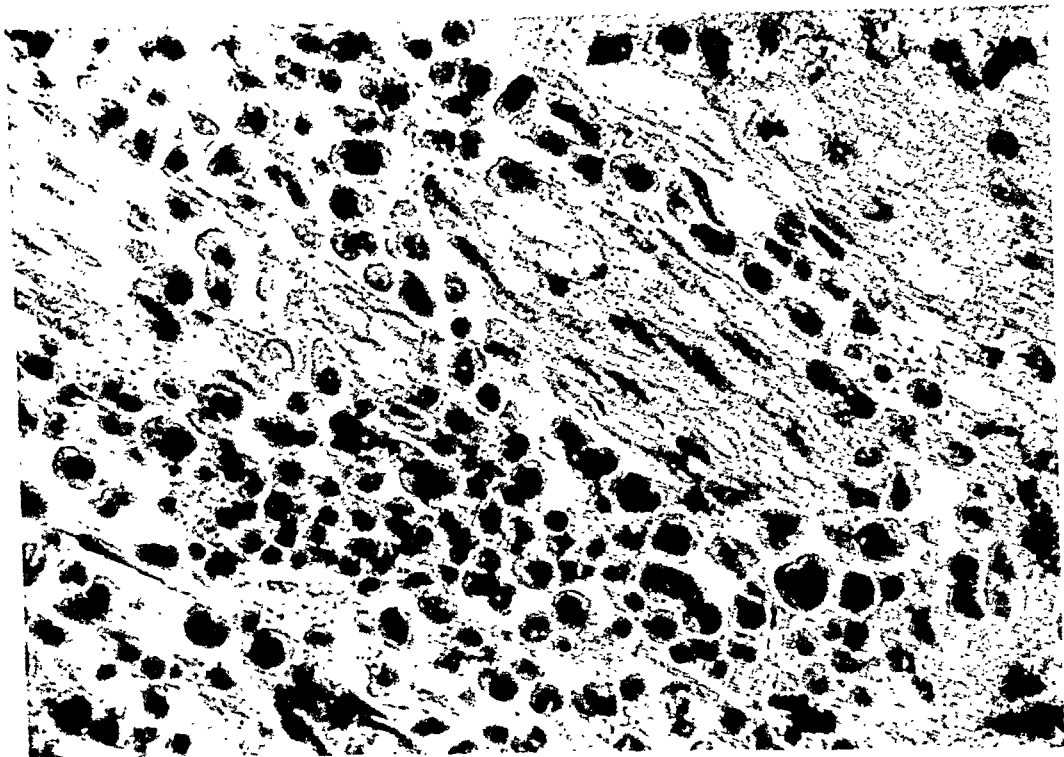
Tooth Buds and Jaws

PLATE 53

FIG. 4. Spirochetes in pulp and predentin. $\times 1140$.

FIG. 5. Spirochetes enclosed within osteocytes of syphilitic periostitis. $\times 1400$.

FIG. 6. Syphilitic reaction in the tooth sac of a syphilitic infant, $1\frac{1}{2}$ months old.
Collection of plasma cells and a few lymphocytes. $\times 700$.



Bauer

Tooth Buds and Jaws

PLATE 54

FIG. 7. Syphilitic productive inflammation in the tooth sac of an infant, 1½ months old, showing plasma cells, lymphocytes, fibrosis and excessive calcification of fibrous tissue. $\times 60$.

FIG. 8. Dense perivascular syphilitic infiltration and collection of exudate in the tooth sac of a syphilitic infant, 1½ months old. $\times 60$.

7



8



Bauer

Tooth Buds and Jaws

PLATE 55

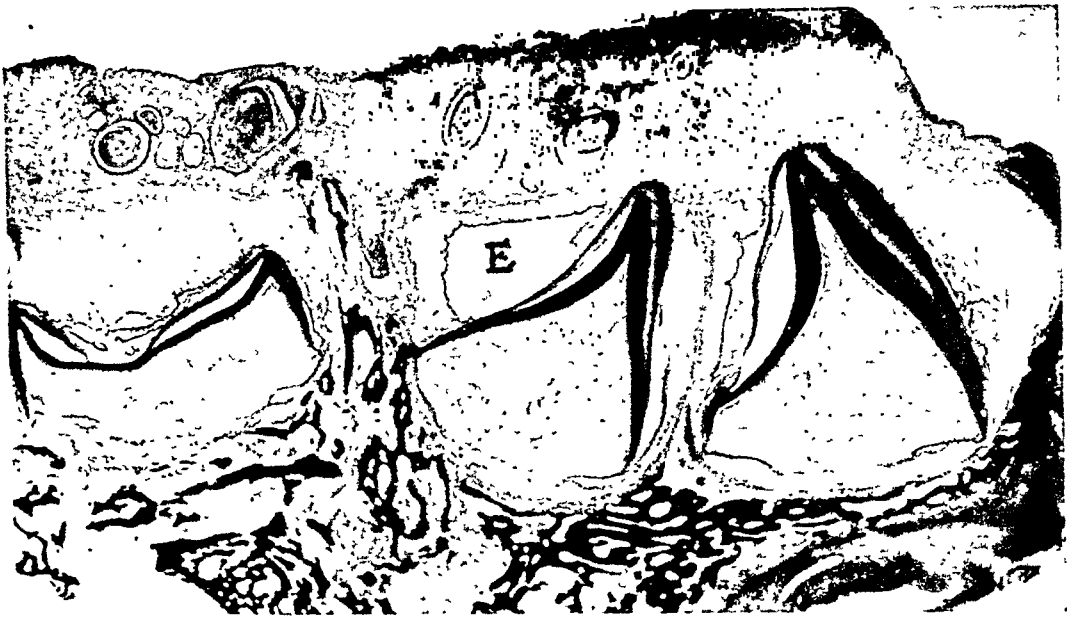
FIG. 9. Mesiodistal section through the deciduous cuspid and molar buds of a syphilitic infant, 1½ months old. E = exudate between enamel and enamel epithelium, which detached and destroyed the latter. Syphilitic inflammatory reaction throughout the bone marrow. $\times 4$.

FIG. 10. From a syphilitic infant, 1½ months old. Abortive enamel (A) and cellular débris between enamel and degenerating ameloblasts. The predentin is of normal thickness and structure. Dentin (D) is well calcified. $\times 70$.

10



9



Bauer

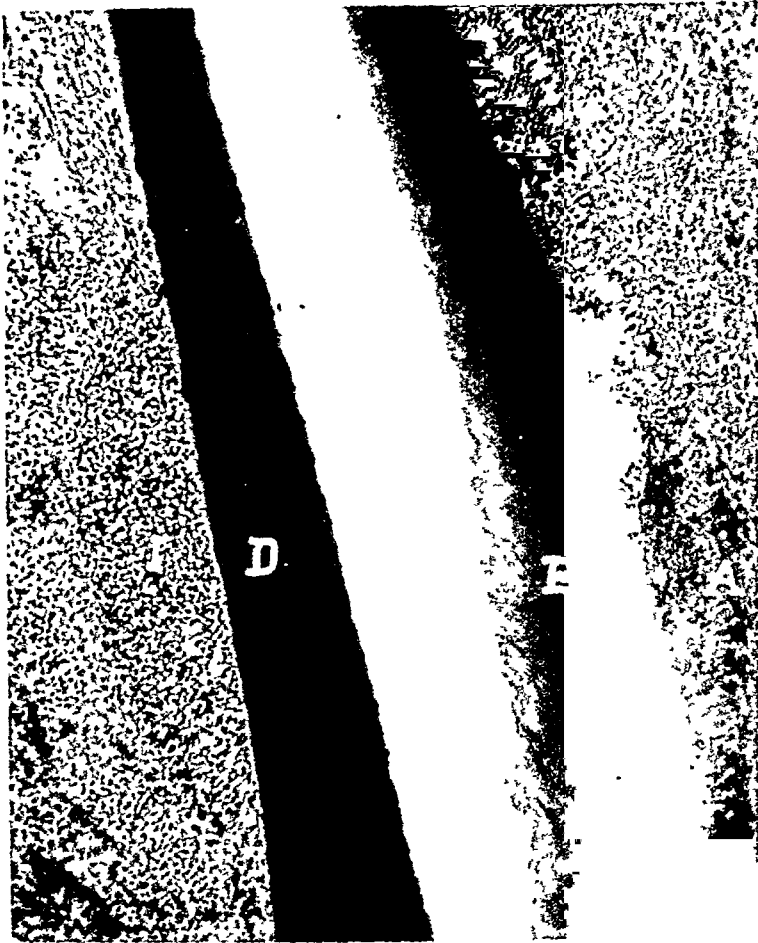
Tooth Buds and Jaws

PLATE 56

FIG. 11. From a syphilitic infant, $2\frac{1}{2}$ weeks old. Accumulation of small round cells with spotty necrosis (I) in the pulp adjacent to the very thin predentin. There is no disturbance of calcification of dentin (D) and enamel (E). Abortive enamel is found between the normal enamel and detached ameloblasts (A). $\times 70$.

FIG. 12. From a stillborn syphilitic fetus, of 9 months' gestation. Productive inflammation in the tooth sac of the lower second deciduous molar. Destruction of Hertwig's sheath. Endosteal formation of fibrous, densely calcified bone encroaching upon the tooth sac and the mandibular canal (C). The bone marrow is replaced by granulation tissue. $\times 40$.

11



12



Bauer

Tooth Buds and Jaws

DEFECT OF ENDOCARDIAL CUSHION DEVELOPMENT AS A SOURCE OF CARDIAC ANOMALY

A PRESENTATION OF FOUR CASES FROM AUTOPSY REPORTS *

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Of the three more common cardiac anomalies, persistent foramen ovale, persistent ductus arteriosus and incomplete interventricular septum, the latter is of the most obscure embryologic origin and most often associated with other examples of anomalous cardiac development. As early as 1814, Farre¹ called attention to the frequency of occurrence of pulmonary stenosis and overriding aorta with defect of the interventricular septum. To explain all defects of the septum as a failure of the septum membranaceum to form normally is to overlook or disregard those cases where concomitant anomalies or the extent and position of the defect forces one to assume a developmental failure of much earlier origin.

It is the object of this paper to present four cases of congenital cardiac anomaly which, though differing considerably in detail and extent, seem best explained as a failure of development, in varying degree, of the ventral endocardial cushion, a structure appearing quite early in the formation of the mammalian heart.

REPORTS OF CASES

Case 1 (Autopsy No. 1481)

The patient was a female infant, 4 months of age (though so small as to appear as newborn). She had six brothers and three sisters living and well. Four days before admission to the hospital the child began to cry frequently as though in pain. She also began to cough, and had a temperature of 104° to 105° F. The child had gained very little weight since birth and also had failed to gain in stature. There was consistent difficulty in feeding. The physical examination showed extensive consolidation in both lung fields, decreased motion of both sides of the chest, and scattered coarse, moist râles.

The heart was removed *en bloc* with the lungs and was not weighed. It was tremendously enlarged, filling (in transverse diameter) three-fourths of the chest cavity. Its largest dimensions were: length, 6 cm.; width, 5.5 cm.; anteroposterior diameter, 3.5 cm.; and circumference, 15 cm. (measured after partial fixation). The right atrium was much dilated as compared to the left; so was the right ventricle, but to a

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lesser degree. There were no serious anomalies of the great vessels other than a large, patent ductus arteriosus and a marked constriction of the aortic arch proximal to its union with the ductus. From this point distally it appeared normal. The pulmonary trunk was small but otherwise normal.

Incision of the anterior wall revealed a large and patent foramen ovale. The interventricular septum appeared intact but thin and with an unusually large, thin septum membranaceum. The atrioventricular valves were normally cusped but of unequal size, the tricuspid valve being almost one-third larger than the mitral valve. Papillary muscles and trabeculae carneae appeared normal.

Further careful examination * revealed an interesting communication between right and left sides of the heart. A channel, 1.1 cm. in length and 0.3 cm. in diameter, led from the left ventricle to the right atrium. Its origin was a slit-like opening in the superior portion of the interventricular septum, below and between the orifice of the mitral valve and that of the aortic root. The course was to the right, posteriorly and superiorly, through the substance of the cardiac septum. The atrial end of the passage was a similar slit, situated on the anteromedial wall of the right atrium just cephalad to the orifice of the tricuspid valve. In life it doubtless formed a communication by which arterial blood from the left ventricle could regurgitate to the right atrium, thus accounting for the hypertrophy of the right heart, the large patent ductus and the under-development of the preductal portion of the aortic arch.

Case 2 (Autopsy No. 738)

The patient was a white male infant, 5 months of age, who weighed 7 lbs. From a few weeks after birth the baby had been cyanotic. He was premature and weighed 3½ lbs. Weight gain was irregular but normal otherwise. Cause of death was given as epidemic cerebrospinal meningitis.

The heart was not weighed because it was removed with the lungs and thymus *en bloc*. The pericardial sac was free of fluid and was everywhere smooth and glistening. The heart was enlarged at least 50 per cent by volume and more by weight; being in systole, the ventricular walls were very thick. There was a rotation to the left which caused the right ventricle to occupy most of the precardial area, with the left ventricle displaced posteriorly. The right atrium was greatly dilated but received superior and inferior venae cavae normally. The

* Credit is due Dr. Elizabeth Conforth for the careful examination of this heart at time of autopsy which revealed the not readily apparent anomaly.

coronary sinus was enormously dilated, covering the lower portion of the left atrium, and received an extracardiac branch from above which ran in the mediastinum on the left side. Its origin was undetermined but it was, presumably, an anomalous superior vena cava (left precordial remnant).

The aorta was found to take origin in the normal location of the pulmonary artery. It was of small caliber and gave origin to an innominate artery which curved upward and to the left. The aorta, from the origin of the innominate to the point of union with the ductus arteriosus, was a very slender segment of 0.2 cm. in diameter. Here the vessel became of normal size and seemed a continuation of the ductus arteriosus. This arch then gave origin to the left subclavian artery and continued downward normally.

The pulmonary artery arose from the left ventricle, bifurcated and proceeded normally, other than for the presence of the patent ductus arteriosus already mentioned.

Internally, the only anomalies were a large opening in the interventricular septum immediately below the orifices of origin of the aorta and pulmonary arteries and a widely patent foramen ovale.

Case 3 (Autopsy No. 1092)

The body was that of a newborn white female. The weight was not recorded, and there was no history available. Anatomical diagnosis: congenital heart disease; interstitial lobular pneumonia.

The heart and lungs were removed *en bloc*. The myocardium seemed more flabby than usual but not hypertrophied. The right ventricle was slightly dilated and the right atrium larger than normal. The tricuspid valve measured 6 cm. in circumference. From the anterior left corner of the base of the right ventricle, a small orifice, 1 cm. in circumference, opened into the pulmonary artery. Opening from the same ventricle, just superior and posterior to the pulmonic valve, was a large orifice, 4 cm. in circumference, leading to the aorta.

A large foramen ovale connected the atria. The left atrium was small. The left ventricle had a small cavity and a wall 0.4 cm. thick. The mitral valve was 5 cm. in circumference. A large septal defect, 2.5 by 1.5 cm., was found in the anterior portion of the interventricular septum just inferior to the region between the openings of the great vessels and the atrioventricular orifices. This was the only opening from the left ventricle, other than the mitral orifice. An adequate septum was found between the aortic and pulmonary trunks. A patent ductus arteriosus was found.

Case 4 (Autopsy No. 250)

The patient was a colored male infant, 8 days of age, who weighed 6 lbs. and 13 oz. The child was apparently normal at birth by cesarean operation, because of a contracted pelvis. The weight was 6 lbs., 8.5 oz. The mother was a primipara and was in labor for 56 hours. On the fifth day of life the child cried and seemed ill. On the following day, he had increasing signs of cyanosis. He vomited just before death 2 days later.

The heart was markedly dilated and somewhat globular. It weighed 25.6 gm.; was 11.0 cm. in its largest circumference; 6.6 cm. in its longest vertical diameter; 5.5 cm. in its longest transverse diameter; and 1.7 cm. in anteroposterior diameter.

A triangular incision in the anterior surface revealed a single atrium and a single, almost undivided, ventricle. The inside transverse dimension of the atrium was 5.1 cm. The superior and inferior venae cavae entered posteriorly. Slightly above the opening of the superior vena cava and 0.6 cm. to the right on the anterior surface was the opening of a single pulmonary vein. To the right of this opening there was a ridge with a few shreds of tissue attached which represented all that had developed of an interatrial septum. A bicuspid valve, 4.6 cm. in circumference, separated the atrium from the ventricle and was the only communication between them. The anterior papillary muscles were small or lacking but the three posterior muscles present were very large; the largest measured 1.5 by 0.5 cm. in its greatest dimensions. All sent their chordae to the same cusp, the large posterior one. There was no division of the common ventricular cavity, but a small ridge on the posterior wall was suggestive of a septum which failed, otherwise, to develop. Trabeculae carneae were prominent.

In the left superior wall of the ventricle was the aortic orifice with three semilunar leaflets. Its circumference was 2.8 cm. A coronary artery was given off posterior to the aortic sinus and had branches to right and left sides, 0.6 cm. from its origin. The pulmonary arteries likewise arose as branches from this common aortic trunk just distal to its emergence from the ventricular wall. A communication, 1.1 cm. in length, connected the point of origin of the right pulmonary artery with the innominate artery, which it reached 0.3 cm. beyond the origin of the latter from the aortic arch. This, obviously, was the unobliterated sixth aortic arch on the right. A second communication between the aorta and left pulmonary artery occurred just distally and was interpreted as the ductus arteriosus. It, too, was patent.

DISCUSSION

In the development of the human heart, the endocardial cushions are among the earliest internal structures to appear. During the fourth

week of fetal life the primitive tubular heart undergoes a simple S-shaped bend due to its relatively faster growth than the space between its points of anchorage by the aortic arches, cranially, and by the septum transversum, caudally. In this stage, three distinct regions are apparent: caudally, the sinus venosus which receives all venous return to the heart; next cranially, the slightly expanded atrium; and most cranially, the major portion, the bulbo-ventricular loop. It is at this time that the future atrioventricular sulcus becomes indicated externally. Internally, in the region of this sulcus, two masses of mesoderm, arising from the mass of the future epimyocardium, appear in the midsagittal plane to lift up the endothelial lining and be covered by it. One arises dorsally, and at about the same time one appears from the ventral wall. These are the endocardial cushions. They grow toward each other to meet and fuse, forming a pillar of tissue which divides the primitive atrioventricular communication into the two future atrioventricular orifices, right and left. In addition, they serve as the caudal line of attachment for the interatrial septum, next to develop, and, during the close of the fifth and beginning of the sixth week, they serve in the same capacity for the cranial margin of the interventricular septum, then being formed.

Very promptly upon the appearance of the endocardial cushions, a pair of ridges appear internally in the cranial or bulbar portion of the bulbo-ventricular loop. These ridges run parallel to the lumen of the bulb and are slightly spiral to the axis of the lumen. Their continued development and fusion form the spiral septum which later divides the bulb into the future pulmonary and aortic roots. If we accept the dynamic theory of Spitzer,* which explains the development of cardiac structures in terms of the dynamics of the fluid which perfuses them, it seems logical that the appearance of these endocardial cushions, particularly the ventral one because of its position, has much to do with the appearance of the bulbar ridges and the bulbar septum which subsequently forms from them. Also, the direction of its formation and, possibly, its ultimate fusion with the interventricular septum are similarly determined. This latter fusion, when completed, wholly separates the primitive heart into right and left halves, except for the normal embryologic continuity through the foramen ovale in the interatrial septum.

If such a significant rôle in development may be ascribed to the endocardial cushions, and particularly to the ventral one because of its proximity to the line of fusion of the septa of the bulb and ventricle,

* For an excellent summary and evaluation in English of the works of A. Spitzer, most of which were published in German from 1921 to 1933, see Harris and Farber.²

it becomes possible to explain the early observation of Farre¹ and likewise the four cases with which this paper is concerned.

In the first case, the channel of continuity from the left ventricle to the right atrium obviously passed through those structures arising from the substance of the ventral endocardial cushion. Here we must assume some inadequacy or interruption of development rather than failure, since septation of this heart was otherwise complete. The large area of the septum membranaceum might indicate a possible retardation of development of the interventricular septum which, however, did not hinder its ultimate completion.

In the second case, that of a heart with anterior defect in the interventricular septum and a transposition of the great vessels, the causes of the anomalies are less evident and, yet, may be inferred in their general outline. The transposition of the great vessels was the result of the spiralling of a bulbar septum in a direction the reverse of that which normally occurs. This reversal is conceivable if we assume that, during the fourth week, the dorsal endocardial cushion appeared but no ventral one grew out to meet it. This unusual condition sufficiently affected the flow of the coursing fetal blood that, though the bulbar ridges and eventually the septum were stimulated to develop, their direction was the reverse of the normal. It is a well known fact that where complementary structures develop, a failure of one is usually compensated, more or less, by overdevelopment of the other. Hence, in the absence of a ventral cushion, the pillar of tissue which divided the primitive atrioventricular communication may have been provided entirely by the dorsal cushion. It is possible, also, that the ventral cushion may have appeared, but too late to assume its normal significance. Once established, the reversed bulbar septum sought its normal union with the interventricular septum; but in the absence (or inadequacy) of what is normally supplied by the ventral cushion, such union could not be complete. Hence we find the large anterior fault in the interventricular septum, a defect occurring not at the septum membranaceum, where final closure of the septum normally occurs, but farther anteriorly and resulting from a failure of origin at a much earlier time.

The third case offers excellent evidence for the assumption that the ventral endocardial cushion plays some rôle in the union of the bulbar and interventricular septa. Each developed; the bulbar septum, completely; the interventricular septum to the region of its normal union with that of the bulb. Dorsally, the cranial extension of the interventricular septum found a normal union with the endocardial pillar, as

shown by the presence of properly positioned atrioventricular orifices, right and left. But the ventral portion of this cranial margin did not find its normal union with the bulbar septum, at that time quite complete. Instead it moved to the left and found attachment to the left wall of the aortic root, which position gave origin to both arterial trunks from the right side of the septum or the future right ventricle. That this failure to fuse normally is due to an absence of tissue supplied by a third contributor, the ventral cushion, is further substantiated by the large fault in the interventricular septum just below the point of normal septal fusion. It may be argued that this interventricular patency was necessary to give egress from the left ventricle to the great vessels since, otherwise, the left ventricle would have been a blind pouch (see description of heart). In part, this is true; yet the large area of the defect suggests that it arose as a developmental inadequacy as well as a physiologic necessity. Such inadequacy seems best explained as a retardation of development of the ventral endocardial cushion during the sixth week of fetal life.

The fourth case is one of complete failure of septation of the primitive heart. That a dorsal endocardial cushion began to form may or may not be indicated by the ridge on the dorsal wall of the common ventricle. In any event there was not sufficient cushion development partially to divide the atrioventricular canal, right and left, hence no bulbar septum formed and neither interatrial nor interventricular septa appeared beyond the initial stages of a septum primum as indicated by the shreds of tissue found on the cranial surface of the common atrium. If this septum primum formed to any extent, it found no endocardial pillar for its caudal attachment and became abortive. There is no indication of a septum secundum appearing unless these shreds of tissue indicate an early development of both septa of the atrium which were later arrested in further development.

The retention of the right sixth arch perhaps served to augment the right pulmonary supply, as did the ductus arteriosus on the left, since pulmonary arteries and aorta had origin from a common, undivided bulb.

The scant development of this heart beyond a primitive fetal stage indicates an early failure of those structures to appear which initiate the later developments leading to final septation—the endocardial cushions. Such failure must have occurred early in the fourth week of fetal life.

SUMMARY AND CONCLUSIONS

Four cases of congenital cardiac anomaly have been presented, ranging in extent from a completely septate heart, with a communication

from the left ventricle to the right atrium, to a primitive, two-chambered heart with undivided atrium and ventricle and a common pulmono-aortic bulb. These cases have been discussed and an attempt has been made to estimate the source and time of failure in fetal life.

From the facts of these cases a few general conclusions seem warranted:

1. The failure of normal endocardial cushion development leads to patency of the anterior portion of the interventricular septum which defect may be associated with anomalies of the great vessels or other structures.

2. The ventral endocardial cushion plays some rôle in the normal union of the interventricular and bulbar septa.*

3. Patencies of the interventricular septum are of two distinct origins: (a) a failure of the septum to close in the region of the future septum membranaceum, and (b) a failure of fusion of the bulbar and interventricular septa due to failure of contribution by the ventral endocardial cushion.

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* Since the completion of this paper, the published observations of Kramer³ support our assumption of the rôle of the endocardial cushion in septation of the bulb and ventricle.

EFFECTS OF POTASSIUM IODIDE ON THE SKELETAL TISSUES OF GROWING MICE *

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In former investigations, we observed ¹ that administration of potassium iodide for 20 days stimulated both proliferation and regression of the epiphyseal and articular cartilages in immature guinea-pigs; it also increased the resorption of the primary bony trabeculae during the growth period. These changes resembled in some respects the early changes found in the cartilage of growing mice and guinea-pigs subsequent to the administration of anterior hypophyseal and thyroid hormones.²

The present investigation was undertaken in order to determine how prolonged administration of potassium iodide influences skeletal development and ageing in mice, and how these effects compare with those obtained by the administration of anterior hypophyseal and thyroid hormones.

MATERIAL AND METHODS

Twenty-eight male mice were used in these experiments. Eight mice of the closely inbred strain C57, 4 weeks old, received intraperitoneal injections of 0.1 cc. of a 2.5 per cent solution of potassium iodide in distilled water. Two of these mice were injected for 4 consecutive days and sacrificed the next day; the remaining 6 mice were injected for 5 consecutive days; no injections were given on the sixth and seventh day. The animals were killed in pairs after 1, 2 and 4 weeks following the first injection. Twenty mice of the closely inbred strain C₃H, 4 to 6 weeks old, were treated in the same way for periods of 4 days, 1, 2 and 4 weeks, and 2, 3, 4, 5 and 11 months. Four untreated male mice of the strain C57 and 10 of the strain C₃H (when possible, littermates) served as controls.

At necropsy, tibia and femur were removed as a whole. The growth zone at the upper tibia was selected for histological study.

* These experiments were conducted in the Laboratory of Research Pathology, Washington University, School of Medicine, St. Louis, Mo.

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OBSERVATIONS

The animals stood the injections well. During the first 2 weeks, the mice injected with potassium iodide gained somewhat less weight than the untreated animals. In strain C57, this deviation from the normal was more accentuated than in strain C₃H. However, after 4 weeks of injection of potassium iodide, there was no difference in the weights of the treated and the control mice.

HISTOLOGICAL EXAMINATION

I. In Strain C57

(a) *Epiphyseal Disk.* After 4 days of injection of potassium iodide, the pattern of the growth zone of 4½-weeks-old mice was regular. In a single row, 4 hypertrophic cartilage cells were counted, as is normal for this age; the columnar cartilage cells were slightly increased in number; there were 10 to 12 instead of the usual number of 10. The nonoriented cartilage cells were rounded off and had undergone noticeable proliferation. The columnar cartilage cells likewise showed increased mitotic proliferation, and their conversion into hypertrophic cartilage cells was intensified.

One week after the beginning of the injections of potassium iodide, the epiphyseal disk was narrower than after 4 days of treatment, and also somewhat narrower than in untreated mice of corresponding age. The mitotic proliferation of the cartilage cells was less accentuated than after 4 days of treatment. In a single cartilage row, the number of columnar cells had fallen to 8 to 10, and that of hypertrophic cells to 2 to 3. Simultaneously, the columnar and hypertrophic cartilage cells had decreased in size, while the cartilage ground substance had increased in amount and the calcification of the cartilage was intensified. Moreover, the cartilage cells had undergone karyolysis and karyorrhexis, conditions not seen in control mice of this age. The conversion of columnar into hypertrophic cartilage cells and the replacement of the latter cells by bone were markedly accentuated.

After 2 and 4 weeks of treatment with potassium iodide, the zone of endochondral ossification showed a distinct narrowing and a heavier calcification than ordinarily. The number of columnar cartilage cells in a single row was 6 to 8 instead of 10, that of the hypertrophic cells was 2 instead of 4. Moreover, regressive changes in the cartilage became conspicuous. Several groups of adjoining cartilage cell-rows were thus affected, and thick plugs of amorphous cartilage appeared in the growth zone of 6-weeks-old mice (Figs. 1 and 2). In healthy untreated animals of this strain, a similar condition is not seen before the end of

the fourth month of life. Resorptive processes had likewise increased and had begun, in some places, to dissolve the amorphous plugs. Perforations of the epiphyseal disk, however, were not observed.

(b) *Subepiphyseal Layer.* After 4 days of injection of potassium iodide, the subepiphyseal zone, in which the replacement of cartilage by bone takes place, was congested. Mitotically proliferating spindle cells and epithelioid cells acting as osteoblasts filled the opened cartilage capsules and the peritrabecular tissue. After 1 and 2 weeks of injection, a partly fibrous, partly osteogenic tissue had developed. Numerous trabeculae containing nonossified or incompletely ossified cartilage were linked with each other by transverse bony bridges, but at the same time resorption of bone became accentuated. The activity of increased numbers of osteoclasts and of enlarged capillaries had caused a shortening of the bony spicules that were thickened in their proximal parts.

After 4 weeks of administration of potassium iodide, a thick transverse bony plate delimited the layer of hypertrophic cartilage cells from the bone marrow in 8-weeks-old mice. This condition is ordinarily not found before the end of the fourth month of life in animals of this strain. On account of the increased resorption of osseous tissue, the excessive amount of trabecular bone found at the earlier experimental stages had disappeared.

(c) *Joints.* During the first 2 weeks of injection of potassium iodide, the articular cartilage proliferated markedly by mitoses and underwent increased hypertrophy (Fig. 3).

After 4 weeks of treatment, the hyperplastic processes had decreased, whereas hypertrophy and ossification of the cartilage were still prominent. These changes were followed by, or associated with, an intensive resorption of cartilage and bone. Karyorrhexis and karyolysis of the articular cartilage cells were pronounced.

(d) *The Bony Shaft.* During the early stages the periosteum was vascular and loose. The spindle cells at the inner and outer surfaces of the compacta proliferated very much, and they were, in greater numbers than ordinarily, converted into osteoblastic epithelioid cells. Thus, both endochondral and periosteal ossification were increased, the maximum being reached after 1 and 2 weeks of injection of potassium iodide.

Following this period, increased cellular and vascular resorption caused a solution of the excessive amount of bony tissue seen at the earlier experimental stages. Thus, the histological structure did not differ from that seen in untreated mice of corresponding age. There were no changes in the bone marrow proper.

II. In Strain C_3H

The skeletal tissues of mice of strain C_3H exhibit ordinarily a faster rate of development and ageing than those of strain $C57$.³

(a) *Epiphyseal Disk*. After injections of potassium iodide for 4 days, the epiphyseal growth zone of mice of strain C_3H , $4\frac{1}{2}$ weeks old, showed a greater narrowing and a heavier calcification, but less stimulation of proliferative processes in the cartilage than the corresponding animals of strain $C57$. In a single cartilage cell-row of strain C_3H , 2 or 3 hypertrophic instead of 4, and 6 or 7 columnar cartilage cells instead of 10, were counted. As in strain $C57$, the conversion of columnar into hypertrophic cartilage cells was intensified, and it began farther proximally than usual. The hypertrophic cartilage cells underwent an accentuated replacement by bone.

After 1 and 2 weeks of treatment, the cartilage cell-rows had shortened still more than after four injections of potassium iodide. The number of hypertrophic cartilage cells in a single row had now fallen to 1 or 2, whereas the number of columnar cartilage cells was unchanged at 6 or 7. The cartilage cells were shrunk and densely calcified (Figs. 4 and 5). The regressive changes had affected several cartilage cell-rows and amorphous plugs of cartilage appeared in the growth zone of mice 5 and 6 weeks old. Breakdown and osseous replacement of the hypertrophic cartilage had progressed so rapidly that after 2 weeks of injections typical hypertrophic cartilage cells were lacking, while the number of columnar cells had decreased to 5. The degenerative plugs had increased in number and extent.

After 1 month's treatment, larger areas of the epiphyseal cartilage had undergone regression and such a degree of calcification that a cell count could not be made. On the other hand, advancing bone marrow began to resorb the amorphous plugs (Fig. 6). Thus, in $2\frac{1}{2}$ -months-old mice of strain C_3H , the structural age of the epiphyseal growth zone was comparable to that of untreated mice of this strain 4 to 6 months of age.

After 2 months of injections of potassium iodide, the conditions were the same as after 1 month.

With prolonged duration of the experiment, the resorption of bone made some further progress, whereas the histological appearance of the cartilage cells had not changed as compared with the preceding stage. Four and 5 months subsequent to the beginning of the treatment, wider perforations of the epiphyseal plate were noted. After 11 months of injection, the structural age of the epiphyseal disk in mice of strain C_3H did not differ from that of control mice of corresponding age.

(b) *Subepiphyseal Layer.* The subchondral lamella separating the epiphyseal cartilage from the bone marrow was laid down as early as 1 week after administration of potassium iodide had begun, whereas in strain C57 a corresponding state was reached only after 4 weeks of treatment.

After 2 and 4 weeks of injection of potassium iodide, the greater part of the spicules had been dissolved, while the transverse bony plate had become more solid.

After 1 and 2 months of treatment, the thick osseous plate had become corroded on its distal side by bone marrow.

After 3 or more months, the subchondral bony lamella had thinned out, and such bony spicules as were still present were likewise in an advanced stage of resorption. After 11 months of treatment, the conditions did not deviate from those seen in noninjected animals of corresponding age.

(c) *Joints.* The hyperplasia of the articular cartilage was less accentuated, whereas hypertrophy and regressive changes were more pronounced than in strain C57. At later stages, resorption of bone was intensified. Hyalinized homogeneous areas were found in the articular cartilage. They apparently had replaced areas of cartilage that had undergone regression.

(d) *The Bony Shaft.* During the early experimental stages, the compacta was thicker than in strain C57, probably due to the greater amount of bone usually present in strain C₃H.

After 2 and 4 weeks of treatment, resorption of bone was more pronounced than was seen in strain C57. After 2 and more months of injection of potassium iodide, the resorptive processes were still more accentuated. After 5 months of treatment and later, the equilibrium between formation and resorption of bone was restored. The cortex showed the usual density and thickness.

COMMENT

In growing mice, the early effects of potassium iodide on the skeleton consist of a stimulation of the growth of the epiphyseal and articular cartilages. Subsequently, regression, calcification, ossification and resorption of cartilage and bone are increased, and the onset of epiphyseo-diaphyseal union is accelerated.

Potassium iodide thus promotes skeletal development as well as ageing (1) by an intensification of the growth processes, which is however, associated with a shortening of the growth period; (2) by an acceleration of the onset and progress of the second phase, in which

regressive changes predominate; and (3) by hastening the beginning of the third phase, the one during which resorption of cartilage and bone are prominent. However, with prolonged administration the ageing effect of potassium iodide decreases, and at later stages the structural age of the skeletal tissues is not different from that seen in normal old mice. Complete epiphyseo-diaphyseal union was not accomplished.

The present investigation on the effect of prolonged administration of potassium iodide thus supplements the observations made previously in immature guinea-pigs injected for 20 days. In these guinea-pigs, the stimulation of proliferation and regression of the cartilage had reached a maximum after 14 days, after which period it returned to normal.

The scanty reports on the effect of iodine on body growth are not in agreement. Cameron and Carmichael⁴ did not observe any influence of sodium iodide on body weight and body length of rabbits and rats. Lipschütz and Morales⁵ reported retardation of growth subsequent to the administration of potassium iodide to rats, but Hooker and Newman⁶ noted no such retardation in mice. On the other hand, acceleration and increase of body growth were found in rats,^{7, 8} chickens,⁹ pigs¹⁰ and sheep.¹¹ In growing guinea-pigs, we observed markedly increased mitotic proliferation of the epiphyseal cartilage after a change to an iodine-enriched diet. According to Hunziker,¹² children given iodine were taller than those kept on a normal diet.

The effects of potassium iodide in our guinea-pigs were much more transitory than in our mice. In the guinea-pigs, the treatment was short in relation to the duration of the growth period; it thus might have been too short to cause a more profound alteration of the curve of skeletal growth and ageing. In our mice, on the other hand, the treatment was extended through a large part of the growth period, and in some animals even far into the second and third phases of skeletal development. Furthermore, strain differences may exist in guinea-pigs similar to those observed in mice. These differences play a rôle in determining the responsiveness of tissues to potassium iodide, and the guinea-pigs used in our previous experiments may have belonged to a less responsive strain.

Mice of the slowly ageing strain C57 showed marked skeletal growth changes after treatment with potassium iodide. Conversely, mice of the more rapidly ageing strain C₃H, whose natural growth capacity was almost exhausted at the time of the beginning of the injections, showed relatively little or no increase of proliferation of cartilage. However,

regression of cartilage and resorption of cartilage and bone, that had been in progress at the beginning of the treatment, could be intensified and accelerated also in mice of strain C₃H.

The effects of potassium iodide on the skeletal tissues in mice and guinea-pigs decreased with prolonged administration. This may be due to an adaptation to this substance as Loeb¹³ and Gray and Loeb¹⁴ have observed to occur in the thyroid of rodents. The data of Mendel and Vickery¹⁵ likewise suggest a gradual decrease in the effectiveness of potassium iodide, although the authors do not comment on this point. Their rats fed with additional potassium iodide showed a greater increase of weight and growth during the earlier stages of the experiments than untreated rats. However, the figures obtained at the end of the experiments were similar in the control and in the treated groups.

The effects of potassium iodide on cartilage and bone are comparable to those caused by the administration of anterior hypophyseal and of thyroid hormones.² The differences that do exist are those of degree rather than of kind. The action of potassium iodide was weaker and of shorter duration: there was less proliferation of cartilage during the first phase, the period of growth; regression of cartilage, characteristic of the second phase, was less enhanced than after treatment with either anterior hypophyseal or thyroid hormones; and while the onset of the third phase, that of predominant resorption, was accelerated, resorption did not progress so rapidly, and it was not so intensified as after treatment with the other two hormones. Moreover, potassium iodide caused less bone formation than did anterior hypophyseal hormone.

Although there exists a certain similarity between the skeletal effects of potassium iodide, anterior hypophyseal and thyroid hormones, little can be said as yet about a corresponding similarity in the mechanism underlying the action of these various substances. Potassium iodide seems to affect the cartilage for the most part directly, and not by way of the thyroid gland; in thyroidectomized guinea-pigs, it stimulates the growth of cartilage almost to the same degree as it does in animals with intact thyroids.¹⁶ Other extrathyroidal effects of iodine have been reported by Chapman.¹⁷ Rats show increased food utilization and water intake subsequent to the administration of potassium iodide as they do after injections of anterior hypophyseal hormone.¹⁸ Furthermore, in young pigs, potassium iodide caused an increased retention of nitrogen,¹⁰ a phenomenon also observed under the influence of anterior hypophyseal hormone.¹⁹ Finally, thyroxin-like effects on metabolism and growth have been obtained with iodized proteins.^{20, 21}

SUMMARY

In growing mice, potassium iodide stimulates the progress of the three phases in the life cycle of the skeletal tissues. It increases temporarily the proliferation of the epiphyseal and articular cartilages, accelerates the onset of regression in the latter and stimulates first the formation and subsequently the resorption of bone. The skeletal effects exerted by potassium iodide thus resemble those caused by administration of anterior hypophyseal hormone and of thyroxin; but they are less marked and more transitory than the latter. As is the case also with various hormones, mice of the slowly ageing strain C57 are more responsive to the administration of potassium iodide than are mice of the more rapidly ageing strain C₃H.

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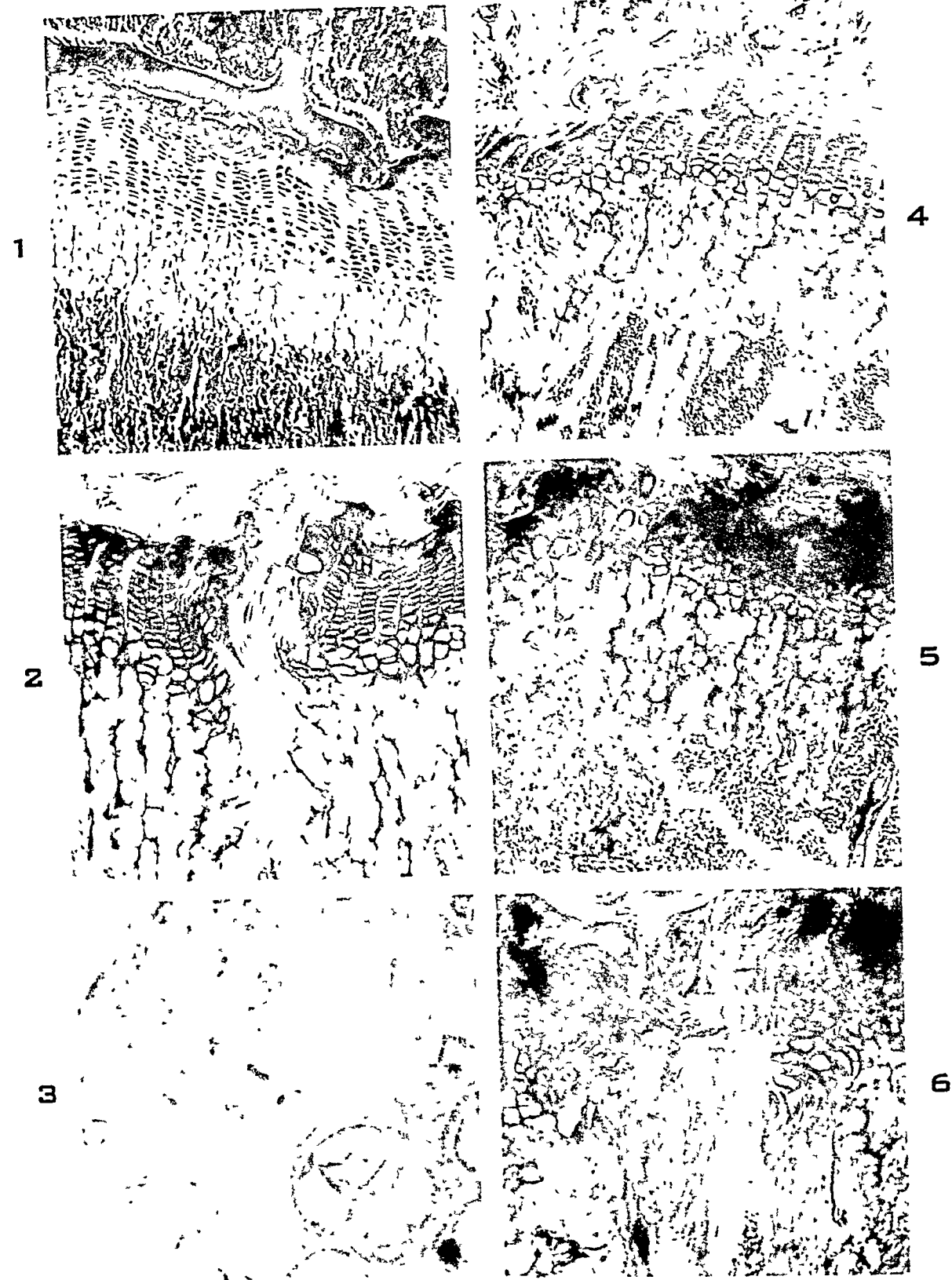
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[*Illustrations follow*]

DESCRIPTION OF PLATE

PLATE 57

- FIG. 1. Section through the growth zone at the upper tibia of an untreated mouse of strain C57, 6 weeks old. Epiphyseal disk shows regular pattern and is wide. $\times 120$.
- FIG. 2. Section through the growth zone at the upper tibia of a mouse of strain C57, 6 weeks old, which, from the age of 4 weeks on, had received injections of 0.1 cc. of a 2.5 per cent solution of potassium iodide five times weekly. As compared with Figure 1, the epiphyseal zone is somewhat narrowed, more heavily calcified and exhibits a thick plug of amorphous cartilage. $\times 120$.
- FIG. 3. Section through the articular cartilage of the lower femur of a mouse of strain C57, which had received four injections of 0.1 cc. of 2.5 per cent solution of potassium iodide starting at the age of 4 weeks. The articular cartilage is hyperplastic and hypertrophic and shows mitotic figures. $\times 500$.
- FIG. 4. Section through the growth zone at the upper tibia of a mouse of strain C₃H, 8 weeks old. Epiphyseal disk narrowed as compared with Fig. 1. $\times 120$.
- FIG. 5. Section through the growth zone at the upper tibia of a mouse of strain C₃H, 7 weeks old, injected for 2 weeks with 0.1 cc. of 2.5 per cent solution of potassium iodide five times weekly. As compared with Figure 4, the epiphyseal growth zone is more heavily calcified, showing formation of a plug of amorphous cartilage. $\times 120$.
- FIG. 6. Section through the growth zone at the upper tibia of a mouse of strain C₃H, 8 weeks old, injected for 4 weeks with potassium iodide. Beginning resorption of the epiphyseal plate by bone marrow. $\times 120$.



Silberberg and Silberberg

Effects of Potassium Iodide on Skeletal Tissues



STUDIES ON AMEBOID MOTION AND SECRETION OF MOTOR END-PLATES

III. EXPERIMENTAL HISTOPATHOLOGY OF MOTOR END-PLATES PRODUCED BY QUININE, CURARE, PROSTIGMINE, ACETYLCHOLINE, STRYCHNINE, TETRAETHYL LEAD AND HEAT *

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The pharmacologist and physiologist have presented chemical and temporal evidence that chemical substances are transmitted from nerve endings to muscle. No morphologic findings are recorded in the literature, however, which support the chemical theory of transmission of the nerve impulse.

A few observations on the histologic changes occurring in the nerve endings under the influence of curare have been made. Kühne¹ described the living nerve endings in the muscle of lizards as having more distinct outlines after deep curare poisoning, and outlines still more distinct after slight curare poisoning and prolonged electrical stimulation of the nerves. Miura² stated that prolonged (18 days) curare poisoning in the frog caused a dwindling in the size of hypolemmal fibers. Herzen and Odier³ found that curare caused the hypolemmal fibers of the frog to become varicose, and the axons of the nerve outside the muscle to become covered with fine granules, the change decreasing towards the center. These early observations practically exhaust the literature of studies on the effect of curare on the histologic structure of motor nerve endings.

Langley⁴ presented a theory which presupposed the presence in the cell of one or more substances (receptive substances) which were able to receive and transmit stimuli, and capable of isolated paralysis, and also of a substance or substances concerned with the main function of the cell (contraction or secretion, or, in the case of nerve cells, the discharge of nerve impulses). Langley stated that his hypothesis demanded that the stimuli passing through the nerve cannot affect the contractile molecule except by means of the radical which combines with nicotine and curare. He concluded as follows:

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"And this seems in its turn to require that the nervous impulse should not pass from nerve to muscle by an electric discharge, but by the secretion of a special substance at the end of the nerve, a theory suggested in the first instance by Du Bois-Reymond."

Du Bois-Reymond⁵ considered the possibility that the excitation of a striated muscle fiber through a nerve fiber might be due to the release of a chemical stimulant when the impulse arrived at the nerve ending. He stated the following:

"Von bekannten Naturprocessen, welche nun noch die Erregung vermitteln könnten, kommen, soviel ich sehe, in Frage nur zwei. Entweder müsste an der Grenze der contractilen Substanz eine reizende Secretion, in Gestalt etwa einer dünnen Schicht von Ammoniak oder Milchsäure oder einem anderen, den Muskel heftig erregenden Stoffe stattfinden. Oder die Wirkung müsste elektrisch sein."

Loewi⁶ had shown that the inhibitory action of the vagus nerve on the heart was associated with a liberation of cardiac depressor substance which had a pharmacologic action on the heart similar to that of choline. He has shown also that the stimulation of the sympathetic nerves was associated with the liberation of an augmentor substance which resembled adrenalin in its action.

Dale and Feldberg,⁷ through experimental evidence, have prepared the way for a consideration of an extension of the transmission of excitation by the liberation of acetylcholine, now long familiar for its peripheral autonomic effects, to all the synaptic and neuromuscular junctions of the peripheral nervous system, whether voluntary or autonomic, with the exception of the peripheral sympathetic fibers which, however, similarly employ an epinephrine-like substance, or sympathin. Brown, Dale and Feldberg⁸ demonstrated that the highly potent acetylcholine was removed immediately by choline esterase. They demonstrated that there was a delay in the disappearance of acetylcholine when the choline esterase action was depressed by eserine.

The mechanism of action of quinine and prostigmine on motor end-plates in myotonia and myasthenia has become important recently in clinical medicine through the studies of the following: Wolf,⁹ Kennedy and Wolf,¹⁰ Kolb, Harvey and Whitehill,¹¹ Curschmann,¹² Weiss,¹³ Pritchard,¹⁴ Lindsley and Curnen,¹⁵ Lindsley,¹⁶ Harvey,^{17, 18} Viets and Schwab,¹⁹ Odom, Russel and McEachern,²⁰ and others. Harvey¹⁷ made the following summary of his observations:

"1. The existing evidence suggests that myasthenia gravis and myotonia are due to abnormalities of neuromuscular transmission. If these are regarded as due to changes in the excitability of the motor end-plates of the muscles involved, the excitability would be lower in myasthenia and higher in myotonia than in the normal muscle."

"2. Quinine has a curare-like action by which it decreases the excitability of the

end-plates. This effect would account for its ability to improve myotonia and to increase the severity of the myasthenic state. Physostigmine and potassium chloride, as would be expected, both produce effects on these two conditions, which are in each case the opposite of those produced by quinine."

Rosenblueth, Lindsley and Morison²¹ assumed:

"That the action of curare consists either in impairing the production of the mediating acetylcholine or in preventing the action of acetylcholine on the muscle, and that the decurarizing agents (physostigmine, adrenine and acetylcholine) antagonize or overcome these possible actions of curare. Thus, if curare made the muscle relatively impermeable to the acetylcholine liberated by the nerve impulses at the nerve endings, adrenine could make it permeable, injected acetylcholine could raise the concentration outside so that sufficient penetration would occur to activate the muscle, and physostigmine could achieve the same effect by preventing its destruction. These assumptions fit the data on hand. They must await, however, further evidence to test their validity."

These assumptions of specific chemical action were in accord with the evidence summarized by Cannon²² which allowed the conclusion that the defatiguing effects of adrenine were not exclusively due to blood pressure changes, but that adrenine also had a specific effect.

In a partially curarized muscle, the excitability of the motor end-plate is lower, so that the response to nerve stimulation is reduced. When quinine is injected under these conditions, the curarization becomes complete. This action is also, in large part, responsible for the abolition by quinine of the quick response of the muscle to injected acetylcholine. Harvey¹⁷ stated that:

"On the whole, however, my results with quinine strengthen my belief that the disturbances in these two diseases [myotonia and myasthenia] are at the motor end-plates. Such a conception gives a reasonably satisfactory explanation of the effects of various drugs on the two conditions; but there is, as yet, no clue to the fundamental processes responsible for the suggested alterations in end-plate excitability."

The studies on the after-potential and retention of negativity in nerve (Amberson and Downing,²³ Gasser and Erlanger,²⁴ Amberson, Parpart and Sanders²⁵) have shown: (a) That reduced polarization of the nerve membrane is associated with hyperexcitability. Gasser and Erlanger found that the phase of supernormal excitability in recovery was present under the conditions which led to the appearance of after-potential, and that the two phenomena seemed to be inseparable. (b) That the passage of impulses reduces the membrane polarization, and can even depolarize it completely in crustacean nerve. (c) That such depolarization occurs readily in the absence of oxygen. (d) That oxygen appears to be necessary for maintenance of the polarization on which transmission of impulses depends, rather than for the actual transmission. Gasser and Erlanger assumed that while the spike

and refractory period are controlled largely by a chemical reaction, the after-potential and supernormality are dependent on the state of the plasma membrane of the nerve. To explain the shortening of the after-potential by cooling, a stabilization of this plasma membrane was proposed.

Through physiologic studies with the oscillograph and amplifier, Matthews²⁶ found that the sensory nerve endings in mammalian muscle spindles may undergo a rapid breakdown and resynthesis under certain conditions of motor nerve stimulation and temporary occlusion of the circulation. He stated the following:

"The rapid discharges which occur in the absence of an external stimulus bear a remarkable resemblance to those recorded by Adrian (1930) from damaged nerve fibres, and suggest that as a result of muscular activity and lack of circulation, the nerve ending breaks down and allows its nerve fibre to behave as though it were cut. One of the most notable features of this phenomenon is that the whole process is reversible, and that recovery from such catastrophic changes in the nerve ending can occur quite rapidly."

Matthews²⁶ furthermore claimed that excitable structures like nerve endings were supposed to generate a propagated disturbance by a breakdown of a polarized surface. The breakdown was followed by a refractory phase and gradual return of the membrane to its normal polarized condition. He gave evidence that when the circulation to a muscle was occluded and the nerve stimulated a number of endings "explode," due to the increased excitability and permeability of the membrane of the nerve ending. When the response of the nerve ending finally stopped due to the restriction of blood supply and high tensions of stretch, Matthews stated this phenomenon was due to a depletion of some substance necessary for repolarization inside the membrane or its accumulation outside, leading to a slowing of the recovery process. These effects were compared by Matthews with the pain occurring in man when work was done by muscles with impeded circulation (Lewis, Pickering and Rothschild²⁷). Matthews stated that pain may be evoked by the rapid discharge from stretch receptors in the muscle spindles.

Morphologic evidence of "explosive" changes in the motor end-plates stimulated by either carbon dioxide or electricity has recently been presented.²⁸

No histopathologic studies have been found in the literature of the effect of myotonia and myasthenia upon the motor end-plates in skeletal muscle. Such study by biopsy should be made after the normal range of variation in the size, shape and internal structure of motor end-plates in man has been established as a morphologic norm

for comparison with any abnormal changes that may be found. The morphologic effects of the chemical action of quinine and prostigmine, as well as other drugs, on the motor end-plates are relatively unknown.

The rapid changes in the pleomorphism of the secretory mechanism of the end-plate may be appreciated by others only if an adequate number of photomicrographs of the results of crucial but simple experiments are presented for study. By this method of presentation of the objective findings others may evaluate the evidence, repeat the experiments, draw their own conclusions. Furthermore, by this method, an extensive descriptive morphology is avoided.

The purpose of this paper, therefore, is the presentation of direct and conclusive experimental morphologic evidence, in the form of easily verified and clear-cut, untouched photomicrographs, that supports the following theses: (1) That the experimental pleomorphism of the hypolemmal axons of the motor end-plates is the result of normal and abnormal functional ameboid motion; and (2) That the experimental variation in the quantity of the granules of the sole plate of Kühne is the structural expression of the differential phases in the secretion of a chemical substance, possibly acetylcholine, from the terminal axons of the motor end-plates.

MATERIALS AND METHODS

The motor end-plates in 10 different groups of muscle (pectoralis major, rectus abdominis, intercostals, erector spinae, biceps brachii, triceps, quadriceps femoris, biceps femoris, sartorius, and gastrocnemius) in the chameleon (*Anolis carolinensis*), weighing 3 to 5 gm., were studied in 230 animals. The chameleon was selected for this experimental study because of the large size and clear-cut components of the motor end-plates. The normal range of variation of the motor end-plates was established for the biceps femoris muscle in 10 animals of the summer chameleon, from May to October (1941 and 1942). The muscles were subjected to various histologic technics such as the Bielschowsky method of silver impregnation as modified by Boeke²⁹ and by the *intra vitam* methylene blue method of Ehrlich as modified by Huber.³⁰ The best method for the study of the continuity of the epilemmal axon, hypolemmal axon, granular sole plate of Kühne and the cross striations of the teased muscle fibers is the modified Ranvier gold chloride technic previously described by me.²⁸ Over 10,000 slides of teased muscle preparations have been made for this study. Boeke claims that the periterminal network revealed in certain motor end-plates by the silver method is the morphologic counterpart of the

hypothetical "receptive substance" of Langley. The granules of Kühne, however, are best revealed in teased muscle fibers after the gold chloride method has been used. Both the hypolemmal axons and the granules of Kühne are profoundly affected by the chemical experiments employed and the histologic method adopted. In fact, the gold chloride method reveals better than any other the pleomorphism of the secretory mechanism of the motor end-plates and supports the statement that these granules could fulfil the function of Langley's receptive and transmitter substance, or they could be granules of acetylcholine or some related chemical substance. Although the hypothesis is advanced that these granules of Kühne may be acetylcholine, to date there is no reliable histochemical technic that has been devised to detect this substance. Pure acetylcholine, as well as choline, produces a granular precipitate with gold chloride in the test tube and a reliable histochemical technic for the detection of acetylcholine, based upon this fact, is now being sought.

The histologic effects on the motor end-plates, in 20 animals, of intocostin (a purified form of curare), 1 mg. per Kg. of body weight injected intraperitoneally, are, within 10 minutes, those of retraction of 50 per cent of the hypolemmal axons and increased staining capacity with gold (Figs. 1, 28, 29, 31, and 46 to 56). The changes produced by the local injection of intocostin (1 mg. per Kg. of body weight) into the biceps femoris muscle of 20 chameleons, followed within 3 minutes by the local injection, in the same site, of quinine hydrochloride (0.5 mg. per Kg.), and, after the lapse of 3 minutes subsequent to the injection of quinine, by another intraperitoneal injection of ammonium hydroxide (0.05 cc. of 1:100), are clearly evident (Fig. 2, and Figs. 73 to 82). The animals died in spastic rigidity within 2 minutes after the injection of ammonium hydroxide. The injection into the peritoneal cavity of prostigmine (1.0 mg. per Kg.) produced expansion in 70 per cent of the motor end-plates in the biceps femoris muscle in 20 chameleons within 5 minutes, at which time the animals were decapitated, the muscles excised and immediately prepared by the gold method (Figs. 3, 11, 12 and 30).

Quinine hydrochloride (0.5 mg. per Kg.) injected into the peritoneal cavity of 20 chameleons produced retraction in 60 per cent of the motor end-plates within 10 minutes, at which time the animals were decapitated, the muscles excised and immediately subjected to the gold method (Fig. 4). Acetylcholine (0.5 cc.; 1:1000) was injected into the peritoneal cavity of 20 chameleons and in 5 minutes the animals were decapitated and the biceps femoris muscle immediately prepared by the gold method (Fig. 5).

When tetraethyl lead (0.1 cc.) was injected into the peritoneal cavity of 20 chameleons the gold-staining material of the motor end-plates was augmented in amount and in staining capacity (Figs. 6, 7, and 83 to 87). Twenty living chameleons, with skin intact, were killed by placing them in Locke's solution at 55° C. for 10 seconds and then in Locke's solution at 4° C. for 1 minute. At 55° C. the animals became rigid within 3 to 10 seconds. Stimulation of the muscle is first through the sensory nerves from the skin and then through the motor nerves of the end-plates. Shortly following this nervous transmission of the heat stimulus, there is direct transmission of heat through the skin to the muscle (Figs. 14 and 15).

Curare (1.0 mg. per Kg.) injected intraperitoneally in 20 chameleons was followed within 5 minutes by the local injection into the biceps femoris muscle of quinine hydrochloride (0.5 mg. per Kg.). This double injection, consecutively timed, was repeated within 2 hours. One hour after the last injection the animals were decapitated, the muscles excised and immediately subjected to the gold method (Figs. 16 to 27). Strychnine sulfate dissolved in Ringer's solution free of HCO_3 and PO_4 was injected into the peritoneal cavities of 20 animals in concentrations of 1:1000 every 6 hours for 48 hours and in amounts of 0.05 cc. at each injection. The animals grossly manifested increased excitability to mechanical tapping throughout the period of 48 hours. They were then killed within 2 minutes by a lethal dose of strychnine injected into the peritoneal cavity (0.5 cc., 1:100), (Figs. 34 to 35).

Prostigmine (1.0 mg. per Kg.) was injected into the peritoneal cavity of 20 chameleons 1 minute after the onset of paralysis from curare (1.0 mg. per Kg.) which had been injected locally into the biceps femoris muscle (Figs. 57 to 59, and 60 to 63). The animals were decapitated 1 minute after the injection of prostigmine. Acetylcholine (0.5 cc., 1:1000) was injected into the peritoneal cavity of 20 chameleons 1 minute after the onset of paralysis from curare (1.0 mg. per Kg.) which had been injected locally into the biceps femoris muscle (Figs. 64 to 68, and 69 to 72). The animals were decapitated within 1 minute after the injection of acetylcholine when they were in a state of strong muscular spasm.

RESULTS: EXPERIMENTAL MORPHOLOGY

1. *The Pleomorphism of the Normal Motor End-Plates*

The length of the normal motor end-plates measured in the long axis of the muscle fibers in the biceps femoris muscle of the decapitated chameleon varied from 20 to 155 μ . The breadth was from 25 to 65 μ and the thickness from 10 to 30 μ . A statistical study of the frequency

in distribution gave the mean for the length of 1000 normal motor end-plates, $87.6\ \mu$, and the mean for the width, $32.9\ \mu$. The mean for the diameter of 1000 muscle fibers was $86.6\ \mu$. The extremes of variation in the diameter of the muscle fibers were from 30 to $170\ \mu$. The morphology regarding size and shape of the motor end-plates in the normal, therefore, was highly variable (Figs. 8, 9, 10 and 13). The amount of the granules in the sole plate of Kühne likewise changed. The granules were condensed in the normally retracted end-plates (Figs. 8 and 9) and they were in close relation to the hypolemmal axon. There was an increased staining capacity for gold. In the normally expanded hypolemmal axons (Figs. 10 and 13) the granules were less in amount and more dispersed. Under these conditions, the granular sole plate of Kühne had a decreased staining capacity for gold. The high coefficient of variation in the size of the motor end-plates in the different fibers of a single muscle and the bizarre shapes assumed by the hypolemmal axons have been explained previously on the basis of functional ameboidism.²⁸ The variations in the amount and staining capacity with gold of the granular sole plate of Kühne likewise were assumed to be due to different phases in the secretory activity of the motor end-plates inhibited by the death of the animals and the histologic technic employed.

2. *The Experimental Ameboid Retraction of Motor End-Plates*

Either curare or quinine produced, in many of the end-plates, an increased staining capacity for gold and an increased amount of granules in the sole plate of Kühne (Figs. 1, 4, 28, 29, 31, and 46 to 51). Quinine appeared to augment the action of curare by the increased retraction, accumulation of Kühne's granules, and staining capacity for gold, of the hypolemmal axon of the motor end-plates (Figs. 16 to 27). By the combined actions, occurring consecutively, of curare and quinine, these end-plates had a more definitely circumscribed border than normally and stood out clearly due to the retraction of the hypolemmal axons and localized condensation of the gold-staining substance. The combined action of these two chemicals appeared to form a dense, impermeable, precipitation membrane which inhibited the dispersion of the granules of Kühne into the protoplasm of the muscle fiber. Within 2 hours after the localized injection of curare followed by quinine, in repeated doses, there was a striking retraction into ball-like and oblong-shaped masses in 65 per cent of the motor end-plates. The mean for the length of 1000 of these motor end-plates was $49.5\ \mu$ (the mean for the normal length was $87.6\ \mu$) and for the

width, $25.4\ \mu$. The mean for the diameter of 1000 muscle fibers was $62.5\ \mu$. Under the combined actions, therefore, of curare and quinine there is a reduction in size of a great number of the motor end-plates which is in contrast to the average increase in size of the motor end-plates in the same muscle but in different animals under the influence of prostigmine. Certain elongated motor end-plates, under the influence of the chemical action of curare during the expansive phase of ameboid motion, had a broad, dense rim of the granules of Kühne. The external border of the granular sole plate of Kühne was in direct continuity with the dark cross striations of the muscle fiber or had a festoon shape influenced by these striations. In some of the expanded end-plates, dense islands of Kühne's granules were found within the end-plate as well as condensed streamers that extended for a considerable distance into the protoplasm of the muscle fiber (Figs. 46 to 51).

3. The Experimental Ameboid Expansion of Motor End-Plates

Within 5 minutes after the intraperitoneal injection of prostigmine, there was an expansion in over 70 per cent of the motor end-plates. The mean for the length of 1000 of these motor end-plates was $110.5\ \mu$ (whereas the normal was $87.6\ \mu$) and for the width, $54.6\ \mu$ in the biceps femoris muscle (Figs. 3, 11, 12 and 30). Fragmentation of the hypolemmal axon into discrete globules was evident in many of the end-plates expanded by the chemical action of prostigmine (Figs. 12 and 30). The morphologic effect of quinine (Fig. 4) was comparable to that of curare (Fig. 1), whereas the action of prostigmine (Fig. 3) was quite comparable to that of acetylcholine (Fig. 5) on the motor end-plates in the biceps femoris muscle. Quinine reduced the average size of the motor end-plates by ameboid retraction of the hypolemmal axons whereas acetylcholine increased the average size of the motor end-plates in the same muscle but in different animals by stimulating the expansive phase of the ameboid motion.

When the living chameleons were plunged into Locke's solution at 55°C . for 10 seconds, and the effect of this short duration of heat was suddenly stopped by plunging them into Locke's solution at 4°C ., there was an expansion of 70 per cent of the motor end-plates. Most of these motor end-plates that had been expanded by heat had a diminution in the amount of immediately related Kühne's granules. These granules appeared to be dispersed into the muscle substance in relation to abnormal waves of heat rigor. Many of these heat rigor waves in the muscle substance were in direct relation to the expanded motor end-plates from which the waves appeared to radiate into the

muscle substance. The chemical action of the dispersed granules of Kühne appeared to influence the morphology of the muscle fiber by the replacement of the coarse cross striations by fine ones closely spaced. The stimulus of heat appeared to have a neoformative influence on the end-plate which underwent ameboid expansion coincident in time with the production of heat rigor in the muscle fiber. The reversible replacement of fine and coarse cross striations in muscle appeared to be the structural expression of the underlying reversible chemical changes of metabolism in normal motion. In abnormal heat rigor, these changes were irreversible.

Radiation of fine cross striations from the motor end-plates was not the result of the mere mechanical approximation of preformed coarse striations. If the motor end-plate had a constant relationship to a fixed number of preformed mechanically static membranes or units called sarcomeres, one would expect to find these striations more widely separated when the end-plate expanded and more closely approximated when the end-plate retracted. The reverse of this, however, appeared to be the case, for the coarse, widely spaced striations occurred in the small retracted end-plate, whilst fine, closely spaced striations occurred in the expanded motor end-plate. This evidence supports the statement that the coarse, widely spaced cross striations were related to the relaxed state of the muscle fiber and the fine, closely spaced ones to the contracted state of the fiber or to the condition of contracture.

4. *The Experimental Material Exhaustion of Motor End-Plates*

When sublethal doses of strychnine sulfate were injected into the peritoneal cavity every 6 hours, for a period of 48 hours, there was a gradual decrease in size of the motor end-plates in the biceps femoris muscle (Figs. 32, 33, and 34 to 45). This prolonged stimulation and chemical fatigue resulted in a depletion of gold-staining substance in both the epilemmal and hypolemmal axons. There was, likewise, a gradual depletion to the point of complete absence of the granular sole plate of Kühne in these exhausted motor end-plates. In fact, the exhausted motor end-plates assumed the morphology of the grape-like terminals (*terminaisons en grappe*) rather than that of the plate-like terminals (*terminaisons en plaque*). The mean for the length of 1000 of these exhausted motor end-plates was $28.4\ \mu$ (whereas the normal was $87.6\ \mu$). The extremes for the length were from $9.5\ \mu$ to $88.4\ \mu$. Wilkinson³¹ thought that the grape-like motor end-plates were immature ones. These grape-like terminals are, however, either the result of exhaustion or quick depletion due to extreme activity and dispersion of granules.

The ramifications and reticulations of the end-plate were highly variable. In some plates there was complete globular fragmentation of the hypolemmal axons. Many of these axonic droplets were discrete and discontinuous with the main group of branches of the hypolemmal axons (Figs. 33 and 38 to 45). The grape-like exhausted motor end-plates were found in 20 per cent of the muscle fibers (Figs. 43 to 45) whereas in the muscle fibers of the normal biceps femoris muscle these depleted end-plates were found in less than 0.25 per cent of the muscle fibers. The striking contrast in size of the epilemmal and hypolemmal axons, and granular sole plate of Kühne, in the nonexhausted motor end-plates and in the exhausted ones (Figs. 43 to 45) is evident. The substantial depletion of the motor end-plates by prolonged stimulation with strychnine was comparable to that produced by the prolonged effect of anoxia caused by carbon dioxide, sodium cyanide, and fatigue due to extensive muscular exercise of the living chameleons.

5. The Experimental Formation of Acute Retention Cysts in Motor End-Plates

When curare and quinine had produced an effective block to neuromuscular transmission, the injection of ammonium hydroxide augmented the gold-staining material in both the epilemmal and hypolemmal axons because of the production of acute retention cysts. Coincident with the formation of these dilated cysts filled with the gold-staining material, there was a diminution in the size of the pseudopod-like hypolemmal axons and in the amount of related granules of Kühne. In fact, around the cysts of the hypolemmal axons there was a complete absence of the granules of Kühne (Figs. 2, 73 to 82). There appeared to be a thickening of the membrane enclosing the dilated cysts in both the hypolemmal and epilemmal axons (Figs. 74 to 77, and 81). By these chemical means, therefore, a mechanical block appeared to be formed to the secretion of the transmitter substance. This was roughly analogous to the damming back of the flowing water in a stream resulting in the formation of a lake. These axonic lakes constitute additional evidence for the thesis that the motor end-plate is a microscopic gland of internal secretion which delivers its chemical product directly into the striated muscle fiber.

6. The Experimental Massive Transmission of Material to the Motor End-Plates

There was a massive conduction of axonic nerve substance into the motor end-plate following the intraperitoneal injection of tetraethyl lead. The animal went into a state of spastic rigidity within 10 sec-

onds. There was a deformation of the hypolemmal axons and an augmentation of gold-staining material in 25 per cent of the motor end-plates (Figs. 6, 7, and 83 to 87). There was a radiation of gold-staining material and a distortion of the cross striations of the muscle substance at the terminals of the abnormal end-plates. The effect of this chemical appeared to be to augment the amount of gold-staining material in the end-plate as well as to inhibit the normal dispersal of this substance. This experimental pathology appeared to be the result of a sudden "explosion" by the rapid transfer of abnormal amounts of the transmitter substance to the end-plate.

7. The Experimental Correlation of Ameboid Motion and Secretion of Granules of Motor End-Plates

The production of the expansive phase of ameboid motion of the hypolemmal axons by either prostigmine or acetylcholine, applied 1 minute subsequent to the failure of neuromuscular transmission induced by curare, resulted in clear-cut morphologic changes (Figs. 52 to 72).

There was an antagonism between the stimulus of expansion produced by prostigmine and acetylcholine and that of retraction produced by intocostin, which resulted in a clear-cut demonstration of the morphology of the expanded hypolemmal axons surrounded by an abnormal increase in the quantity of the granules of Kühne. In some examples there was a more gradual dispersion of the granules of Kühne into the cross-striated substance of the muscle fiber. There was a direct transformation, in some places, of the hypolemmal axons into granules of Kühne (Figs. 55 to 59, and 62). Agglutinated streamers of the granules of Kühne were in many places cross-striated, augmented in staining capacity for gold, and found extending from the terminals of the motor end-plate into the protoplasm of the muscle fiber. The quantity of granules and the morphology of the sole plate of Kühne, therefore, were not constant, fixed and preformed structures surrounding the hypolemmal axons. The transformation of the hypolemmal axons into granules of Kühne was made evident by the stimulus of prostigmine and acetylcholine to ameboid expansion of the hypolemmal axons and by the inhibition to the dispersal of these granules of Kühne by the chemical action of intocostin. In many places, the hypolemmal axon underwent globular fragmentation and granulation.

This relationship of ameboid motion and granular secretion of the motor end-plates was comparable to those observations made by Korschelt³² on the ova and secreting cells of insects, by Heidenhain³³ on

the nuclei of the cells of the salivary glands, and by Huie³⁴ on the profound changes in the nuclei during increased activity of the secreting cells of the insect-eating marsh plant, *Drosera*, when the latter is fed egg albumin. The comparative histologist is familiar, therefore, with this relationship of ameboid motion and secretion.

Korschelt³² studied chiefly the ova and secreting cells of insects. In the egg-tubes of the ovaries of *Dytiscus marginalis*, a large water-beetle, the ova are arranged in succession like a string of pearls and separated from one another by a so-called nutrient chamber. This chamber consists of cells which produce and give off nutrient material to the ova. The behavior and the position of the nuclei of the ova toward this nutrient material is very characteristic. From the chamber the nutrient material extends into the ovum in the form of a granular mass and there disposes itself in such a manner that it comes into very close contact with the nucleus. But the most interesting fact is that which makes the activity of the nucleus toward the nutrient material apparent; namely, that the former sends pointed, pseudopodium-like processes into the granular mass where the latter touches it, and only in this direction, and thus very greatly increases the surface at the place of contact with the nutrient material. If the latter completely surrounds the nucleus, the whole surface shows pseudopodium-like processes. Korschelt described a similar phenomenon, especially in regard to the nucleus, in a whole series of arthropod and coelenterate ova. The interesting behavior of the nuclei in secreting cells toward the secreted substances forms a counterpart to these phenomena of the ingestion of substance on the part of the nucleus. Here certain relations exist toward the substances produced, which are wholly analogous to those existing in ova toward ingested substances. In the eggs of certain water-bugs, *Nepa* and *Ranatra*, there occur peculiar chitinous appendages, the so-called egg-rays, which are formed by cells especially differentiated for this purpose. These cells, of which each two unite into a single cell with two nuclei, termed by Korschelt a double cell, assume a considerable size and secrete within their body a mass of chitin. The behavior of the two nuclei in this process is very characteristic. They send out toward the middle, where the secretion is taking place, numerous, frequently branched, pseudopodium-like processes, which increase the nuclear surface upon this side very considerably, while the rest of the surface remains smooth. Such enlargements of the surface of nuclei are widespread in the secreting cells of insects and show that the exchange of substance between protoplasm and nucleus in secretion must be very active.

Baum³⁵ found that the nuclei of resting gland cells stained much more deeply with nuclear stains than the nuclei of gland cells that had secreted strongly. This was a histologic sign that the chromatic nuclein was destroyed in secretion. In this study on motor end-plates, the differential staining capacity of the components of the motor end-plate for gold may be, likewise, a histologic sign of variations or differential phases in the secretory activity of the gold-staining granules of Kühne of the motor end-plates.

SUMMARY

The experimental pleomorphism of the hypolemmal axons of the motor end-plates is a result of normal and abnormal functional ameboid motion. The experimental variation in the quantity of the granules in the sole plate of Kühne is the structural expression of the differential phases in the secretion of the chemical substance, possibly acetylcholine, from the terminal axons of the motor end-plates. There is a correlation between ameboid motion and the secretion of granules which had been designated, collectively, in the past as the granular sole plate of Kühne. These aurophilic granules of Kühne may be increased in quantity by chemical reagents, such as curare and quinine, which inhibit the adequate dispersal and dissolution of the secreted granules into the protoplasm of the muscle fiber. Neuromuscular transmission is blocked by the action of curare and quinine on the motor end-plates through ameboid retraction of hypolemmal axons and the formation of a dense and circumscribed precipitation membrane composed of the granules of Kühne. The aurophilic epilemmal and hypolemmal axons undergo acute dilatations through the sudden formation of retention cysts produced by the chemical action of curare and quinine followed by that of ammonium hydroxide, which excites substantial transmission to the end-plates. The secreted granules of Kühne may be decreased in quantity to the level of complete depletion by prolonged chemical stimulation such as that produced by strychnine, sodium cyanide, carbon dioxide, and exhausting muscular exercise. Under conditions of exhaustion, in addition to the absence of the granules of Kühne, there is an abnormal decrease in the size of the epilemmal and hypolemmal axons. The terminal expansions of the hypolemmal axons of the end-plate may undergo direct transformation into the secreted granules of Kühne, without the presence of the intervening clear space, by sudden stimulation with either prostigmine or acetylcholine after the end-plate has been blocked by the local action of curare. Heat produces a sudden expansion of the end-plate and a

dispersal of the granules of Kühne that together produce perturbations in the pattern of the cross striations of the muscle fiber. These waves of contracture or rigor appear to be produced by the dispersal of some chemical substance transmitted by the motor end-plate. Tetraethyl lead produces a sudden and explosive transmission of an abnormal quantity of aggregates of aurophilic granules which results in massive radiations, distortion and increased staining capacity of the end-plates for gold. There are, likewise, abnormal distortions of the related cross striations of the muscle fiber to these abnormal end-plates produced by the chemical action of tetraethyl lead. The hypolemmal axons of the end-plate and the related granules of Kühne and cross striations of the muscle fiber are not preformed, static, and fixed in morphology. Their size, shape and internal structure are correlated with physiologic and pathologic secretory activities of neuromuscular transmission.

I wish to express deep gratitude to Mr. Leo Massopust, Director of the Department of Art and Photography, for aid with the photomicrographs; to Dr. G. Kasten Tallmadge, Assistant Professor of Anatomy, for reading the manuscript; to Messrs. John Schmitz, James Keyes, Robert Jeub, Joseph Hamel and Eugene Haushalter for technical aid in the teasing of muscle and nerve plates; and finally to Dr. H. Sidney Newcomer, Medical Department, E. R. Squibb and Sons, for the intocostin used in these experiments.

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[Illustrations follow]

DESCRIPTION OF PLATES

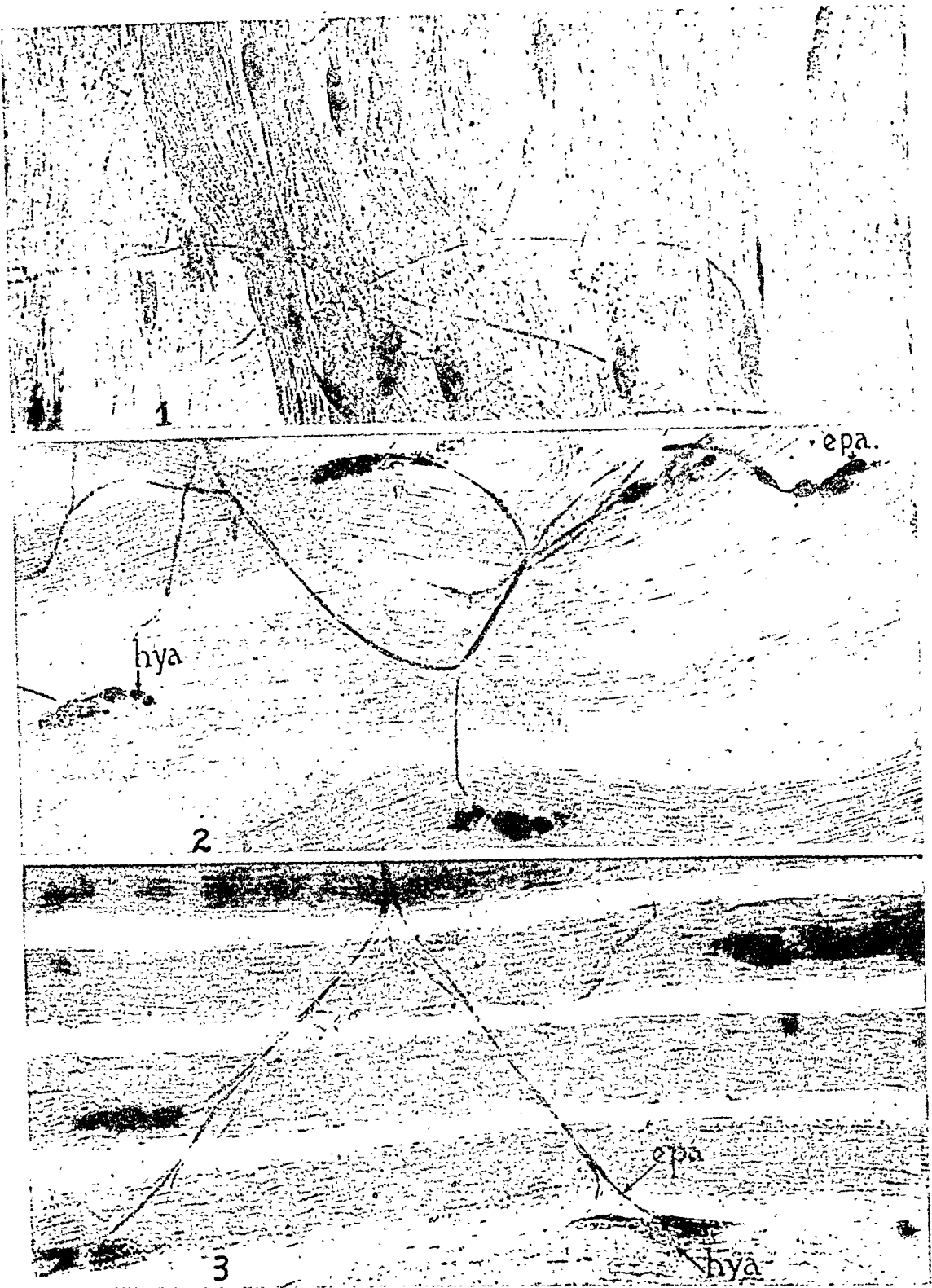
The photomicrographs of Plates 58 to 75 are from the teased whole muscle fibers (biceps femoris) and motor end-plates of the summer (May to October) chameleon (*Anolis caroliniensis*). These teased preparations of motor end-plates in skeletal muscle were previously prepared by the gold chloride technic. The photographs were prepared as direct contact prints from the negatives which were photographed under the microscope and not subjected to subsequent enlargement. In this manner, these photographs are easily comparable with those of the white rat previously published.²⁸ In the plates, "epa." means epilemmal axon and "hya." hypolemmal axon. There has been no retouching of either negatives or prints.

PLATE 58

FIG. 1. Sprays of medullated nerve fibers and motor end-plates which are retracted as a result of the intraperitoneal injection of intocostarin (curare). By centripetal retraction of amoeboid motion the end-plates vary in size from 24 to 85 μ measured in the long axis of the muscle fiber. The axis cylinders vary from 1 to 12 μ in diameter. $\times 125$.

FIG. 2. Sprays of medullated nerve fibers and motor end-plates with acute cystic retention of the gold-staining axonic substance in both the epilemmal (epa.) and in parts of the hypolemmal (hya.) axons. This acute cystic retention was produced by first injecting intocostarin locally into the biceps femoris muscle and 3 minutes later injecting locally quinine hydrochloride. Three minutes after the last injection, ammonium hydroxide was injected into the peritoneal cavity. These relatively simultaneous actions of a chemical block to the secretion of the transmitter substance and the stimulating action centrally by the ammonium hydroxide resulted in the sudden accumulation of the axonic liquid substance into dilated cysts, 10 to 40 μ in diameter, of the axis cylinder both in the epilemmal and hypolemmal axons. The axis cylinder varies from 1 to 40 μ in diameter. $\times 125$.

FIG. 3. Sprays of medullated nerve fibers and motor end-plates expanded by the action of prostigmine injected into the peritoneal cavity. By the centrifugal expansion of amoeboid motion the surface area of the motor end-plates under the action of prostigmine is greatly increased. This morphologic change aids in the dissemination of the transmitter substance from its point of origin in the end-plate and its dispersion throughout the muscle fiber. The axis cylinder varies from 1 to 18 μ in diameter. The motor end-plates vary from 40 to 185 μ in length measured in the long axis of the muscle fiber. The value of the gold chloride technic in preserving the anatomic continuity of the epilemmal axon, hypolemmal axon, ramifications of the terminal axons, the granules of Kühne and the muscle striations is demonstrated not only in Plate 58 but in all of the subsequent illustrations. $\times 125$.



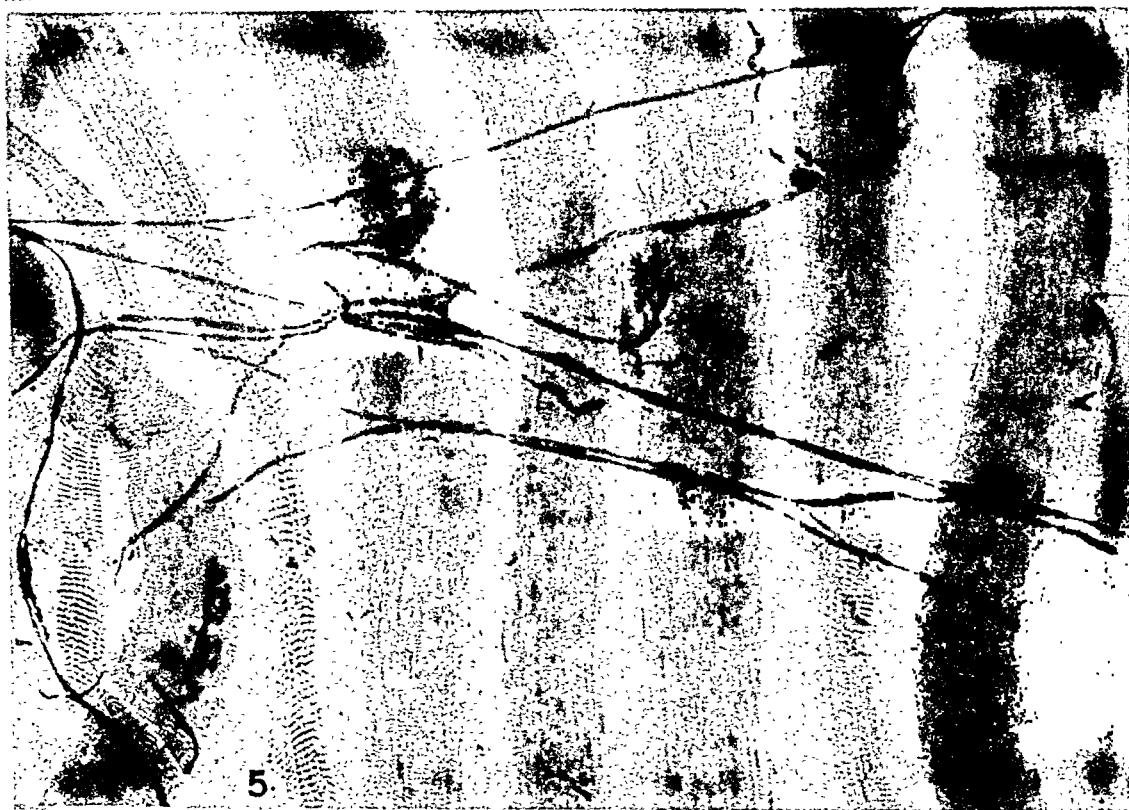
Carey

Motion and Secretion of Motor End-Plates

PLATE 59

FIG. 4. Retraction of motor end-plates under the influence of quinine sulfate injected intraperitoneally. The motor end-plates vary from 35 to 85 μ in length, measured in the long axis of the muscle fiber. These end-plates have an intense affinity for gold and have in many places sharply defined, well circumscribed borders. Many of the muscle fibers are narrow in diameter, granular and coarsely cross-striated. The axis cylinders vary from 1 to 18 μ in diameter. $\times 125$.

FIG. 5. Sprays of medullated nerve fibers and motor end-plates in the state of centrifugal ameboid expansion produced by the intraperitoneal injection of acetylcholine. The axis cylinders vary from 1 to 22 μ in diameter. The motor end-plates with multiple ameboid ramifications vary from 50 to 205 μ in length, measured in the longitudinal axis of the muscle fiber. Most of the muscle fibers are wide in diameter and have fine, closely spaced cross striations. Two of the fibers toward the left (Fig. 5) are narrow and coarsely cross striated, with a zone of transition into fine cross striations at the upper end of each fiber. These stimulated motor end-plates have a greater number of terminal dichotomous divisions than the retracted ones under the influence of either intocostrin or quinine (Figs. 1 and 4). Acetylcholine excites neurocladism or the production of new ameboid projections of the end-plate. $\times 125$.



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Motion and Secretion of Motor End-Plates

PLATE 60

FIGS. 6 and 7. The motor end-plates are distorted with enormous accumulations of the axonic substance which has an intense affinity for gold. This effect is produced by the intraperitoneal injection of tetraethyl lead. There are radiation rays extending from the terminals of these distorted end-plates, which plates vary in length from 80 to 285 μ . In the right half of Figure 7, one axis cylinder has three branches, two of which terminate in expanded plates and one in a distorted end-plate intensely stained with gold chloride. The epilemmal axons vary from 1 to 25 μ in diameter. $\times 125$.



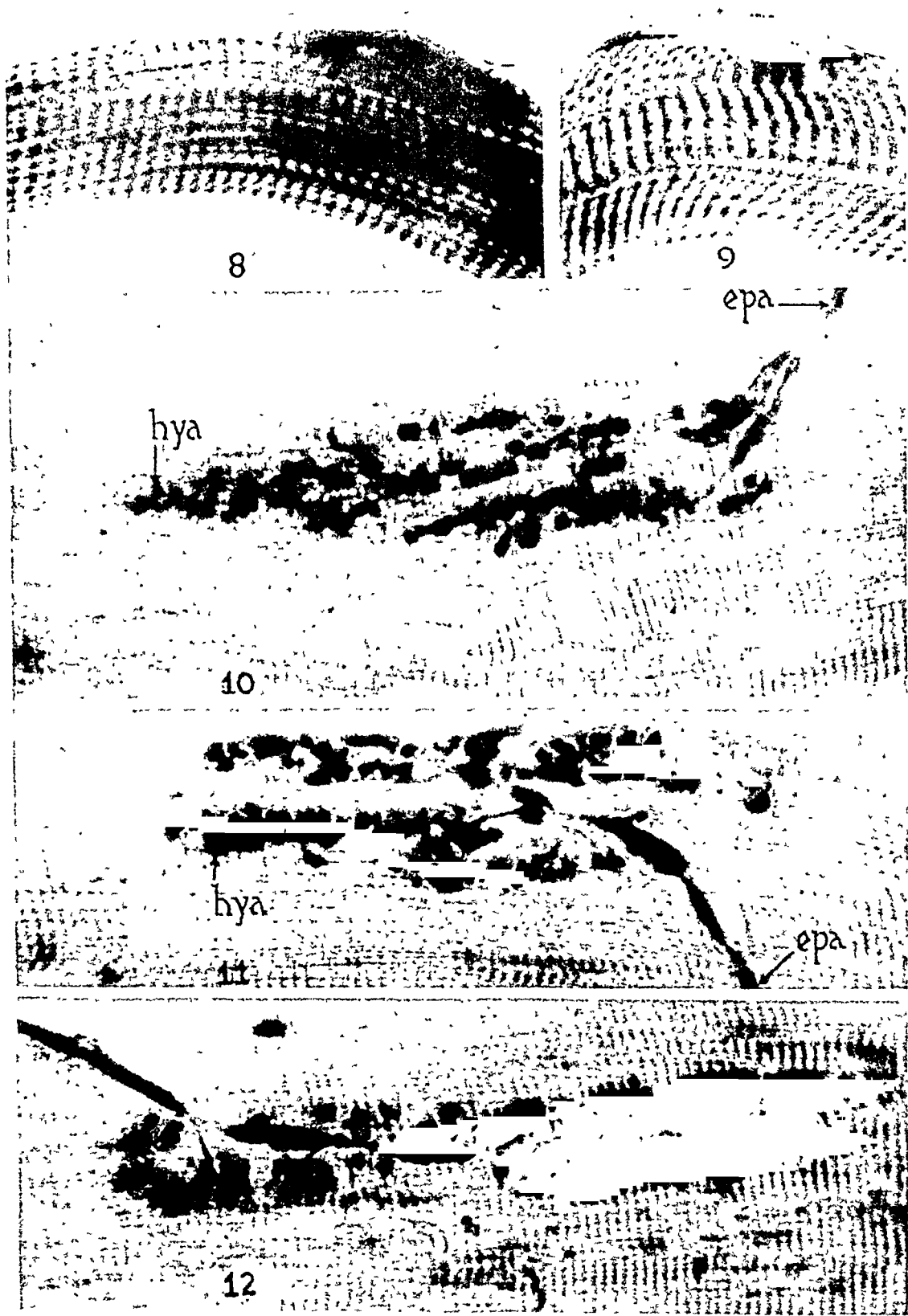
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Motion and Secretion of Motor End-Plates

PLATE 61

FIGS. 8 to 10. Normal teased biceps femoris muscle fibers of the chameleon. The narrow muscle fibers with coarse cross striations (Figs. 8 and 9) have retracted motor end-plates with strong affinity for gold chloride. The wider muscle fiber in the same muscle (Fig. 10) has an expanded end-plate with multiple ramifications to which are related fine, closely spaced, cross striations. The expanded nerve plates in the active muscle fiber have variable degrees of amoeboid extensions of the terminal arborizations of the axon. The hypolemmal (hya.) axons in some of the end-plates terminate in rounded or oblong swellings peripherad to which there may be a light halo-like space around which are found the granules of Kühne. The quantity of the granules in the sole plate of Kühne is highly variable, from the point of complete absence of granules to that of the accumulation of a considerable quantity of the granular material. The granules of Kühne, therefore, are a highly inconstant part of the morphology of the end-plate even in relatively normal muscle. The granules of Kühne are in direct continuity with the dark, anisotropic cross striations of the muscle fiber. The retracted motor end-plates (Figs. 8 and 9) vary from 50 to 60 μ in length and have, respectively, 18 and 16 related dark bands of the cross striations. The elongated end-plate (Fig. 10) is 150 μ in length and has 71 related dark bands of the cross striations. $\times 750$.

FIGS. 11 and 12. Expanded motor end-plates influenced by the intraperitoneal injection of prostigmine. Another type of expanded end-plate (Fig. 30) is likewise characteristic of the effect of prostigmine, which appears to influence the centrifugal phase of expansion of amoeboid motion as well as fragmentation of the hypolemmal axons into droplets of gold-staining globules. Although the granular sole of Kühne is present in many places, it appears to be undergoing rapid dispersal throughout the muscle fiber. The granules are not accumulated into densely stained islands and membranes as they are under the influence of intocostin (curare) and quinine. $\times 750$.

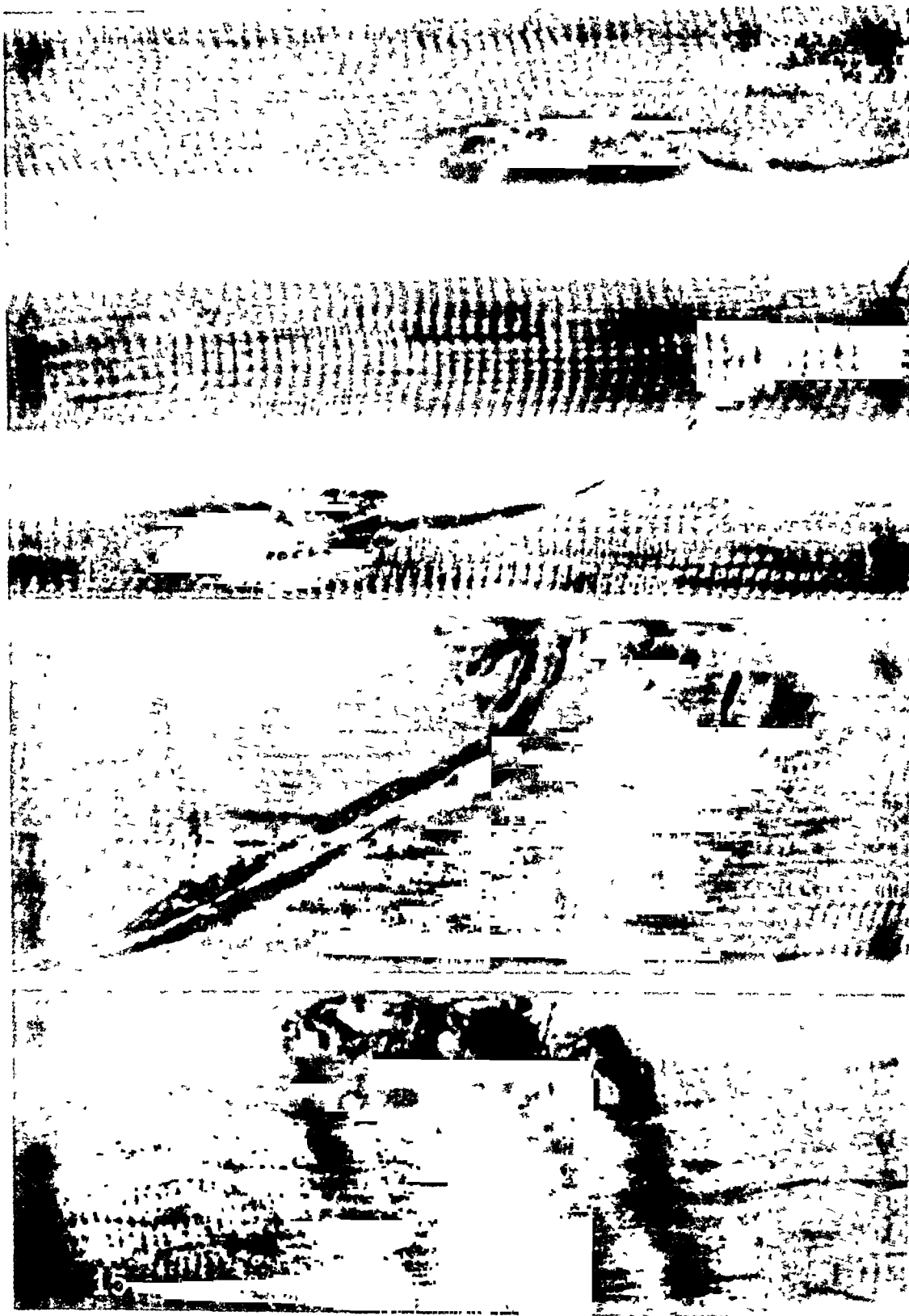


Carey Motion and Secretion of Motor End-Plates

PLATE 62

FIG. 13. Two normal motor end-plates in narrow, coarsely striated fibers of the biceps femoris muscle. There are found variable degrees of splitting of the coarse striations into finer ones in these fixed muscle fibers. The axis cylinders vary from 1 to 15 μ in diameter. $\times 750$.

FIGS. 14 and 15. Radiations of fine, closely spaced cross striations from motor end-plates quickly fixed after the living animal, with skin intact, was subjected to 55°C. for 10 seconds and was then immediately plunged in Locke's solution at 4°C. The motor end-plates, expanded by sudden changes in thermal energy, have the surrounding granules of Kühne undergoing dispersal and in direct continuity with the wave of fine cross striations radiating from the expanded end-plates. The chemical action of the dispersed granules of Kühne appears to influence the morphology of the muscle fiber by the replacement of the coarse by the fine cross striations. The transmitter substance secreted from the end-plates appears to have a profound effect on the morphology of the cross striations. This Leisegang phenomenon in a capillary space, such as that of a muscle fiber, is dependent upon temperature and on the concentration and composition of the chemical reactions. If the cross striations were preformed, constant in number and fixed in structure, and in relation to the motor end-plate, one would expect that when the so-called sarcomere is shortened during contraction the motor end-plates likewise would be shortened mechanically. The fact is that the stimulus of heat has a neoformative influence on the end-plate which undergoes ameboid expansion during the time when the muscle fiber contracts. There are a great number of fine, closely spaced striations in relation to the expanded motor end-plate. This evidence points to the fact that the fine striations of contraction and heat rigor rapidly replace the coarse ones of relaxation, and, furthermore, that the fine striations are not the mere mechanical approximation of the coarser ones. This reversible replacement of fine and coarse cross striations of contraction and relaxation respectively, giving the appearance of a shuttle-like shift, is the structural expression of the reversible chemical changes of metabolism. This occurs with flash-like rapidity and may easily mislead the observer to the conclusion that during contraction there is a mere mechanical approximation of constantly fixed and preformed membranes. $\times 750$.

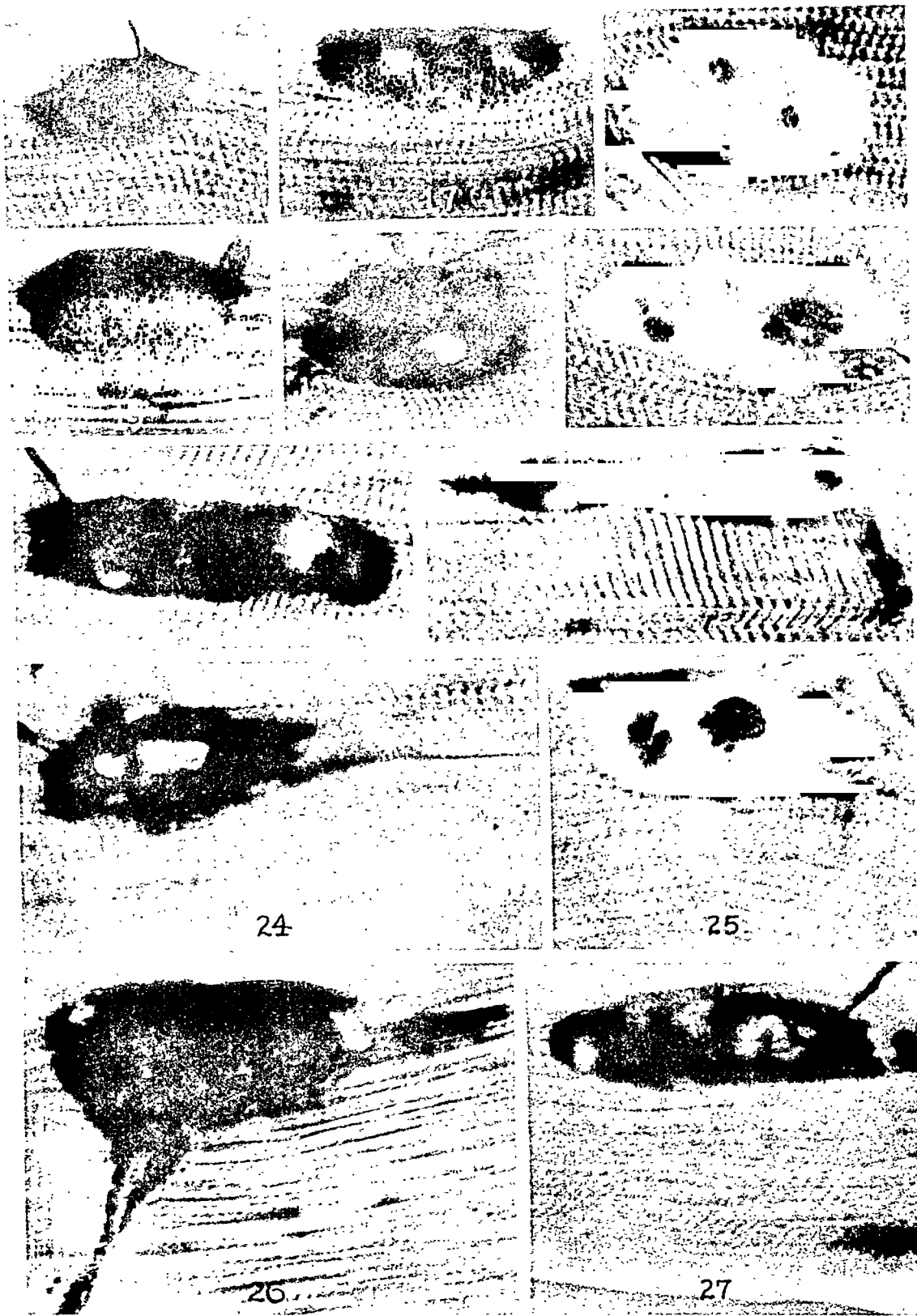


Carey

Motion and Secretion of Motor End-Plates

PLATE 63

FIGS. 16 to 27. Greatly retracted motor end-plates in the biceps femoris muscle after the injection of intocostarin locally into the muscle and of quinine sulfate into the peritoneal cavity. These retracted end-plates have a well defined circumscribed border and an intense affinity for the gold chloride. This is morphologic evidence of a localized increase in concentration of the aurophilic substance both within the terminal axons and in the region of the granular sole plate of Kühne. These granules form a condensed precipitation-membrane which gives the clearly defined border of the motor end-plate. This failure of dispersal of the secreted granules of Kühne by the chemical combination with both intocostarin and quinine, which have a strong astringent action, leads to a condensed membrane formation. The light vacuolar spaces are occupied by nuclei of the granular sole plate of Kühne. Streamers of condensed granules of Kühne are found to the right in Figures 24, 25 and 26. There appear to be conclusive findings of a morphologic nature correlated with the physiologic block in neuromuscular transmission produced by both curare and quinine. $\times 750$.



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Motion and Secretion of Motor End-Plates

PLATE 64

FIG. 28. Retracted motor end-plate in the biceps femoris muscle of the chameleon after the intraperitoneal injection of intocostarin. Both the epilemmal (epa.) and the hypolemmal (hya.) axons are increased in diameter from 1 to 20 μ . In the crotch of the divided hypolemmal axon there are dense islands of the granules of Kühne. $\times 750$.

FIG. 29. Expanded motor end-plate in the biceps femoris muscle with large fragmented globules of the hypolemmal axon after the intraperitoneal injection of intocostarin. There is a clear space between the expanded terminals of the hypolemmal axon and the granular sole plate of Kühne. $\times 750$.

FIG. 30. Expanded motor end-plate with centrifugal projection of ameboid processes and globular fragmentation of the hypolemmal axon after the intraperitoneal injection of prostigmine. In some locations there are isolated droplets of the hypolemmal axon which are completely disconnected from the main axonic network. The hypolemmal axons are thinner and have relatively less accumulation of the granules of Kühne than those under the influence of either curare or quinine. $\times 750$.

FIG. 31. Duplex motor end-plate in a biceps femoris muscle that was first under the influence of curare injected locally into the muscle, and, 2 minutes later, excited by prostigmine injected into the peritoneal cavity. In the hypolemmal axon which appears to be secreting granules of Kühne, the axon becomes more attenuated and less in diameter than in those in which there appears to be (Figs. 28 and 29) either a failure of secretion or of dispersion of the granules of Kühne. $\times 750$.

FIGS. 32 and 33. Motor end-plates of the biceps femoris muscle in which there is a gradual depletion of gold-staining substance in both the hypolemmal axons and granules of Kühne. These granules are practically absent (Fig. 33) after prolonged stimulation with repeated injections of strychnine sulfate over a period of 48 hours. These two end-plates were taken from neighboring muscle fibers in the same muscle. There is progressive decrease in size in both the epilemmal (epa.) and hypolemmal axons (hya.) which is morphologic evidence of exhaustion of the transmitter substance by prolonged chemical stimulation. There is complete fragmentation of the hypolemmal axons in many places into droplets (Fig. 33), around which there is either a great reduction or a complete absence of the granular sole plate of Kühne. $\times 750$.

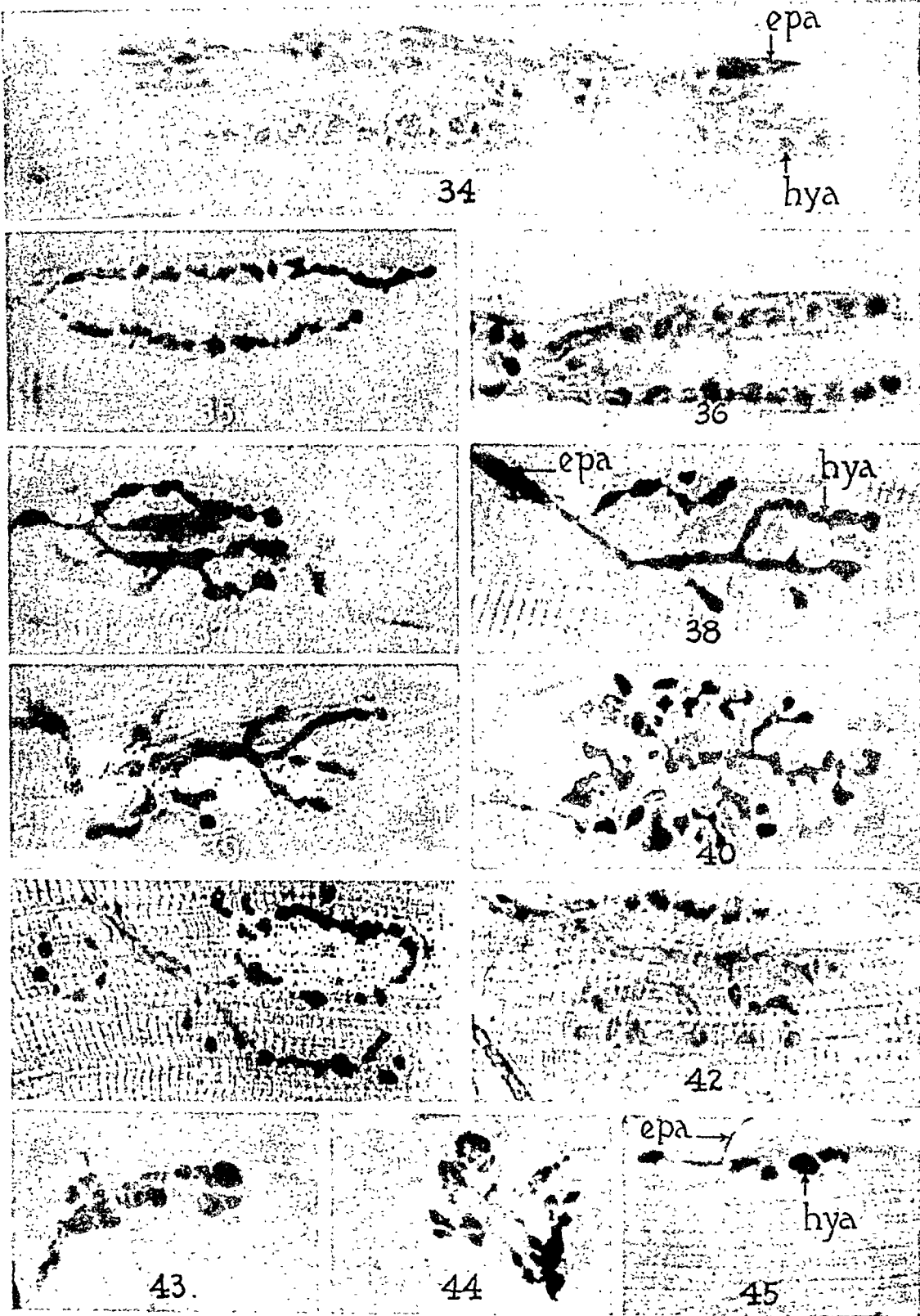


Carey

Motion and Secretion of Motor End-Plates

PLATE 65

FIGS. 34 to 45. Gradual depletion in the amount of the aurophilic substance in the epilemmal axons (epa.), hypolemmal axons (hya.) and granular sole of Kühne, in the biceps femoris muscle after repeated injections of sublethal doses of strychnine sulfate over a period of 48 hours, terminating in a lethal dose. These motor end-plates appear to be formed by ameboidism during super-functional stimulation. The motor end-plates undergo protoplasmic streaming in a centrifugal direction into the muscle substance. The pleomorphism is as variable as that of the pseudopods of an ameba. There are dichotomous branchings and anastomotic reticulations of the terminals of the hypolemmal axons in the end-plate. In many places, the globoid and oblong terminals are completely pinched off from the main trunk of the hypolemmal axon. This progressive decrease in the amount of the gold-staining substance in the motor end-plates to the point of practically complete absence of Kühne's granules is morphologic evidence of a substantial depletion of the transmitter substance leading to exhaustion by the prolonged abnormal stimulation with strychnine. The droplet endings with an absence of Kühne's granules (Figs. 41 to 45) give a morphologic appearance of one type of motor end-plate classified by morphologists as the grape-like ending (*terminaisons en grappe*) in contrast to the plate-like ending (*terminaisons en plaque*). These endings of axonic droplets, however, were produced by exhaustion through prolonged chemical stimulation. They represent depletion of both the axonic and granular substances by abnormal stimulation. Certain endings in normal muscle that are devoid of the granules of Kühne may represent a stage in which the granules are quickly dispersed. $\times 750$.

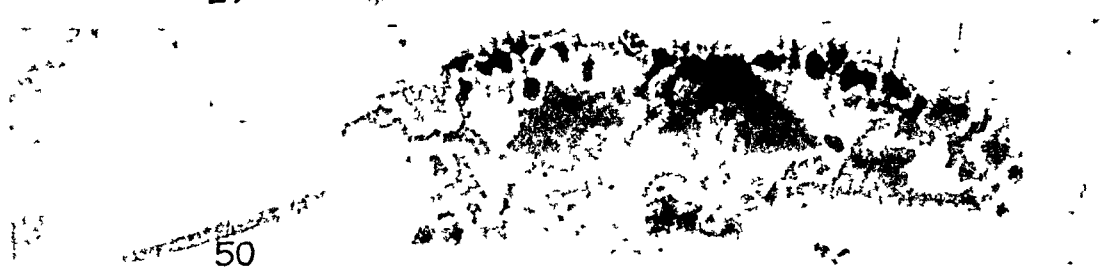
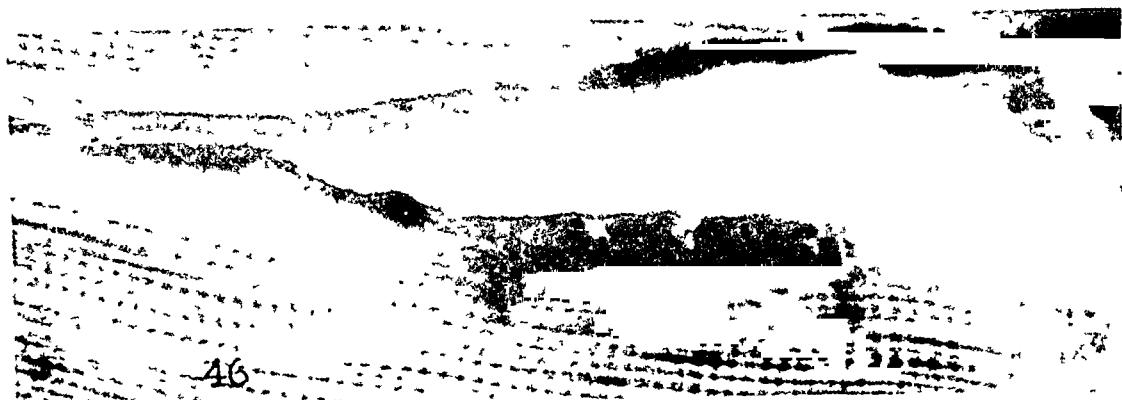


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Motion and Secretion of Motor End-Plates

PLATE 66

FIGS. 46 to 51. Types of retracted and expanded motor end-plates produced by the intraperitoneal injection of intocostirin. The physiologic block to neuromuscular transmission is correlated with a failure of dispersion of the transmitter substance, or the granules of Kühne, from the motor end-plate to the substance of the biceps femoris muscle fiber. There is an abnormal accumulation of the condensed granules of Kühne into a thickened precipitation-membrane surrounding the hypolemmal axons of the end-plate. The accumulated granules of Kühne in the majority of the end-plates have a well defined, circumscribed border from which radiate the dark cross striations. This is evidence of failure of dispersion of the granules of Kühne into the muscle substance. In some of the end-plates (Figs. 47, 48 and 49) the definite border of the sole plate of Kühne is scalloped by the continuous relationship of the dark cross striations. Physiologic block by curare, therefore, appears to be due to an accumulation through failure of dispersal of the granules of Kühne secreted from the terminals of the hypolemmal axons. In some end-plates (Figs. 47 and 50) there are elongated and agglutinated streamers of the granules which appear to be condensed, *in situ*, by the chemical combination with curare. Curare appears to form a precipitation-membrane of Kühne's granules. This inhibits the normal transmission by diffusion and dispersion of this fulminate-like nervous substance that is secreted from the hypolemmal axons and that normally excites the muscle substance by this chemical transmission of nerve impulses. $\times 750$.

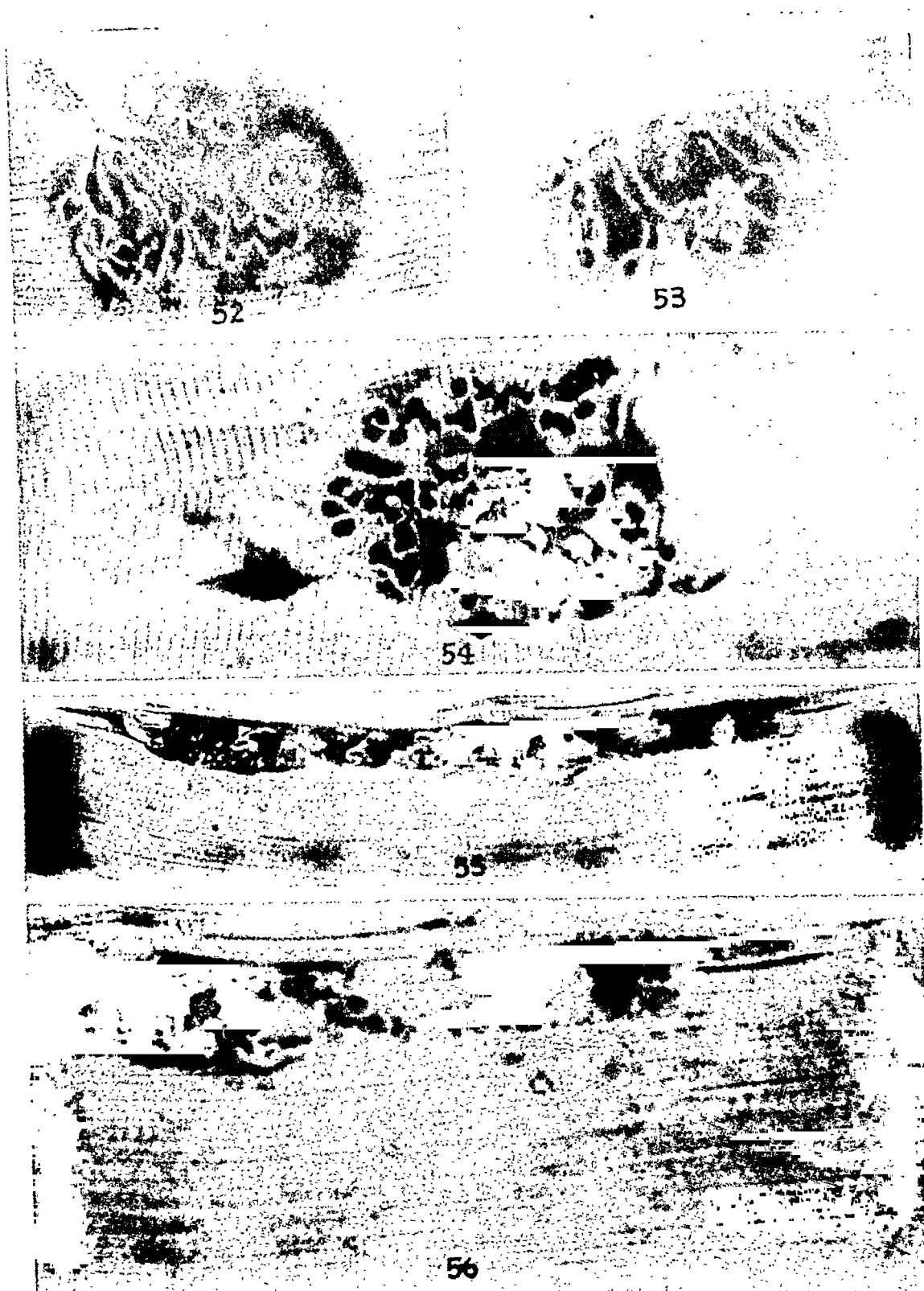


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Motion and Secretion of Motor End-Plates

PLATE 67

FIGS. 52 to 56. Pleomorphism of motor end-plates in the biceps femoris muscle. Intocostarin was injected into the muscle locally and 1 minute later prostigmine was injected into the peritoneal cavity. There is an abnormal accumulation of the secreted granules of Kühne around the hypolemmal axons. Streamers of the secreted granules of Kühne which failed to disperse normally are produced by the chemical combination with curare (Figs 54 to 56). The gradual transformation of the globular terminals of the hypolemmal axons into Kühne's granules is evident in the right half of the illustrations (Figs. 55 and 56). There is a gradual transition from left to right of clear-cut hypolemmal axons surrounded by light spaces into the granular material of the elongated sole plate of Kühne without the intervening clear halo-like spaces. At the left (Figs. 55 and 56) the islands of concentrated Kühne's granules take an intense stain with gold comparable to that of the terminals of the axon. There is an antagonism between the stimulus of expansion produced by prostigmine and the stimulus of retraction produced by intocostarin which results in the clear-cut morphology of the hypolemmal axons and abnormal accumulation of the granules of Kühne. This is morphologic evidence that the terminal axons in the end-plate are microscopic endocrine glands. Their secretion motivates the muscle fibers by a transmitter substance—the granules of Kühne. A precipitate comparable to that of Kühne's granules is produced, *in vitro*, by the chemical interaction of either acetylcholine or choline with gold chloride. At the present time there is no good histologic test for either acetylcholine or choline at the myoneural junction except possibly that of gold chloride. Most other histologic methods destroy the granular sole plate of Kühne. The motor end-plates (Figs. 52 to 72) were obtained from the same biceps femoris muscle after the local injection of intocostarin into the muscle and prostigmine into the peritoneal cavity. (Fig. 55 magnified 300 X; Figs. 52, 53, 54 and 56 are 750 X).



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Motion and Secretion of Motor End-Plates

PLATE 68

FIGS. 57 to 59. Greatly expanded motor end-plates in the biceps femoris muscle.

This pleomorphism followed the injection into the muscle of intocostarin and later the injection of prostigmine into the peritoneal cavity. There is an abnormal accumulation of the granules of Kühne (Fig. 57) and a gradual transition of the hypolemmal axons (Figs. 58 and 59) into the granules of Kühne without the intervention of the clear halo-like space. There appears to be a direct transformation of the terminals of the hypolemmal axons into the secreted granules of Kühne through the violent chemical excitation produced by prostigmine and of inhibition by curare. There is a more gradual dispersion of the granules of Kühne into the substance of the cross-striated muscle fiber than that produced by the chemical action of either quinine or curare. The expansion effect on the motor end-plate produced by prostigmine appears to neutralize partially the microscopic changes in the motor end-plate produced by either curare or quinine acting alone. These antagonistic chemical actions give favorable evidence of the transformation of the axon into the specific secreted transmitter substance. The granular sole plate of Kühne, therefore, is not a constant, fixed and preformed structure. $\times 750$.



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Motion and Secretion of Motor End-Plates

PLATE 69

FIGS. 60 to 63. Pleomorphism by ameboid motion of the axonic branches in the motor end-plate in the biceps femoris muscle of the chameleon. Intocostrin was injected into the muscle locally and 1 minute later prostigmine was injected intraperitoneally. The chameleon died in violent spasm 2 minutes after prostigmine was injected. There is an accumulation of the granules of Kühne around the hypolemmal axons which have undergone, in many instances, globular fragmentation. These droplets vary from 4 to 15 μ in diameter. The clear oval spaces in the granules of Kühne are occupied by nuclei. This blocking of the dispersal of Kühne's granules by curare, followed relatively soon by chemical excitation with prostigmine, results in neurocladism or dichotomous division of the branches of the axon in the end-plate. This centrifugal extension and separation of the terminal branches in the end-plate and the simultaneous block to the dispersal of the granules of Kühne result in the abnormal accumulation of these granules around the related axon. The gradual replacement of the axon directly into the granules of Kühne is observed in the lower and right aspect of the end-plate in Figure 62. To the left and right of the end-plate (Fig. 63) there are elongated streamers of the granules of Kühne that have been agglutinated by the chemical retraction action of intocostrin and projection action of prostigmine. $\times 750$.

60

61

62

63

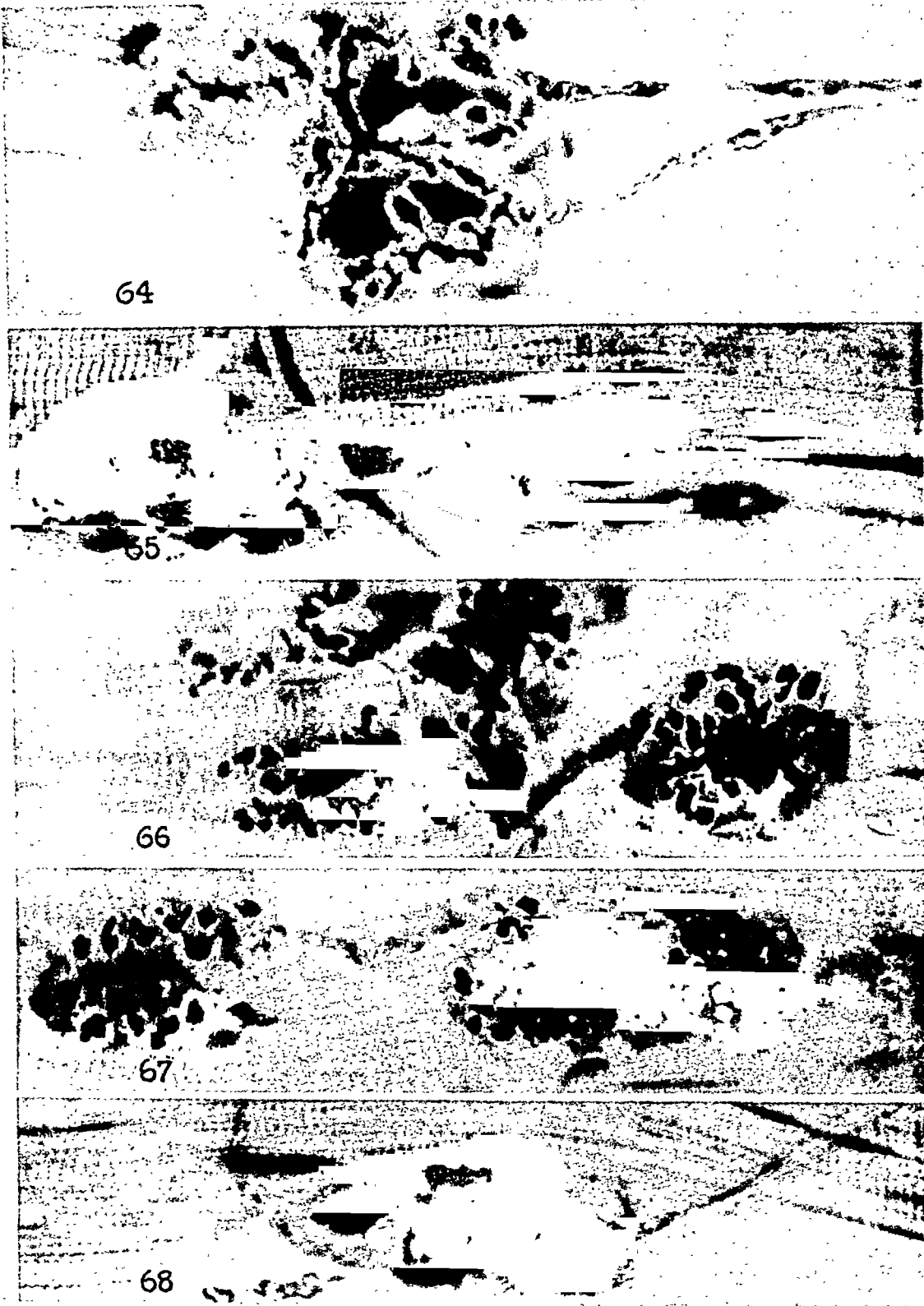


Carey

Motion and Secretion of Motor End-Plates

PLATE 70

FIGS. 64 to 68. Various stages in the expansion and globular fragmentation of the hypolemmal axons and the accumulation of the surrounding granular sole plate of Kühne. Intocostarin was injected into the muscle locally and 1 minute later acetylcholine was injected intraperitoneally. The chameleons were decapitated in violent spasm 1 minute after acetylcholine was injected. The pleomorphic changes in these motor end-plates are the results of mutual antagonism of curare and acetylcholine. The curare partially blocks the transmission of the granules of Kühne into the muscle substance resulting in abnormal accumulations around the branches of the axons and agglutinated streamers of these granules in the muscle substance. The acetylcholine excites the expansive phase of the ameboid motion of the hypolemmal axons. The granules of Kühne (Figs. 65, 67 and 68) have a more intense affinity for the gold chloride than the dark bands of the cross striations in the muscle substance. $\times 750$.



Carey

Motion and Secretion of Motor End-Plates

PLATE 71

FIGS. 69 to 72. Pleomorphism of the hypolemmal axons of the motor end-plates produced by the chemical action of intocostirin followed by acetylcholine. Intocostirin was injected locally in the biceps femoris muscle of the chameleon and 1 minute later acetylcholine was injected in the intraperitoneal cavity. These end-plates were from the same muscle as those fibers illustrated in Plate 69. There is an abnormal accumulation of the granules of Kühne into insular masses found between the axonic branches as well as streamers of these granules projected away from the end-plate (Figs. 69 to 71). These granular streamers represent inadequate dispersal of the transmitter substance which is secreted from the hypolemmal axons into the muscle fiber. Globular fragmentation of the hypolemmal axon is clearly evident in the elongated end-plate (Fig. 72). $\times 750$.

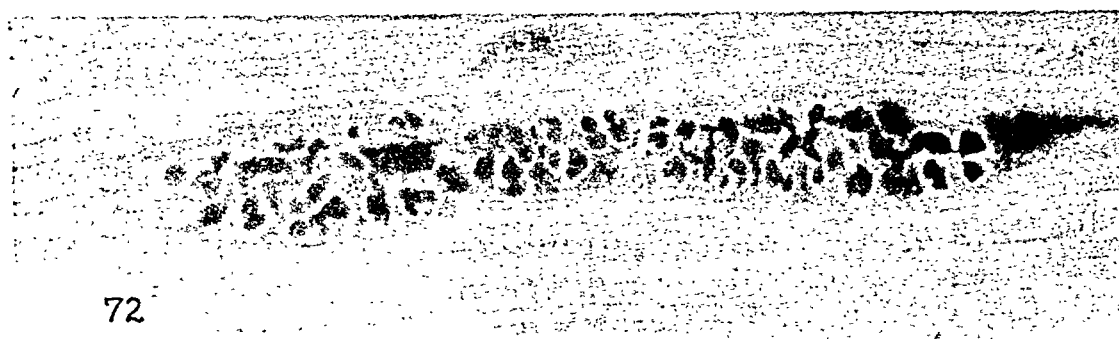
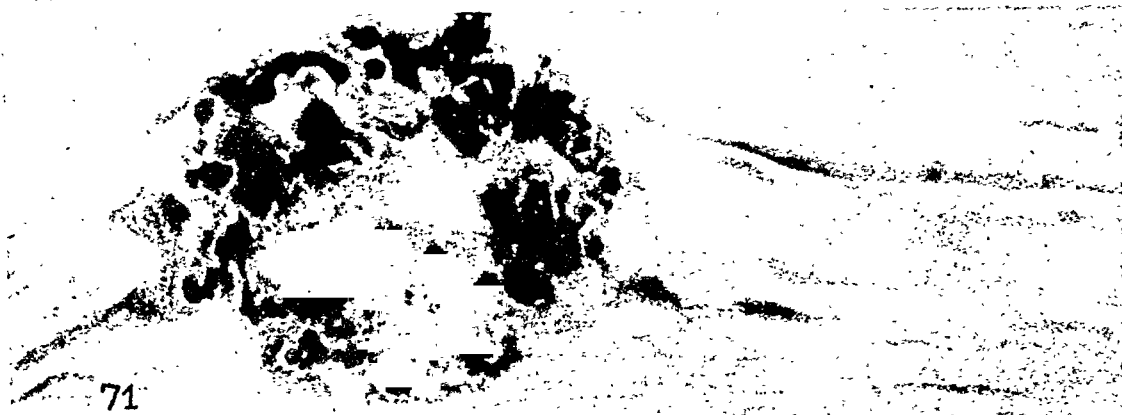
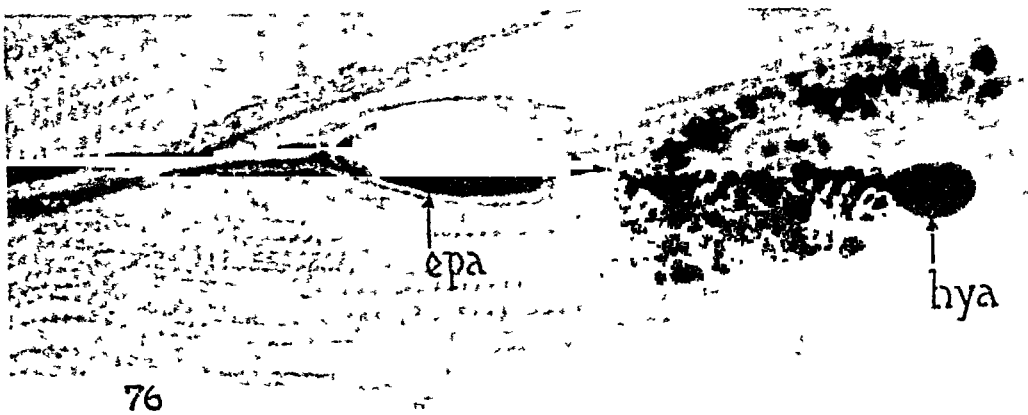
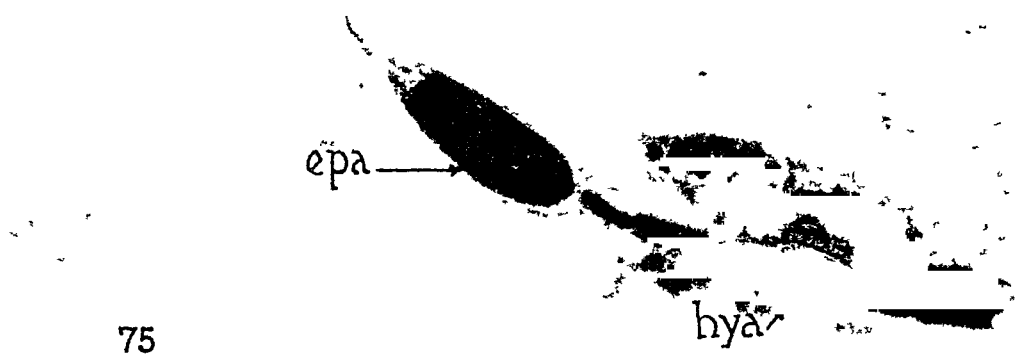


PLATE 72

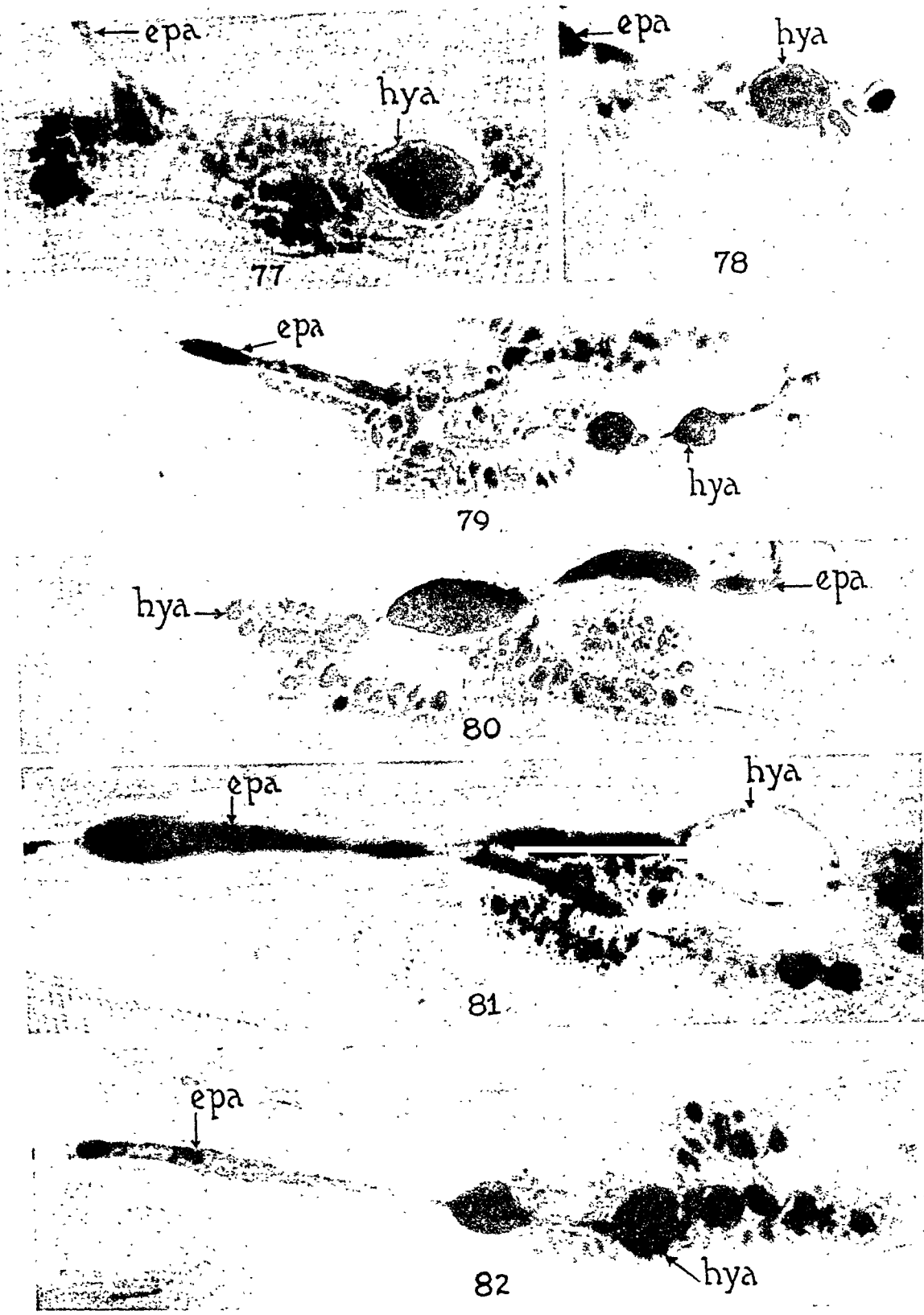
FIGS. 73 to 76. Pleomorphism of the epilemmal (epa.) and hypolemmal (hya.) axons of motor end-plates in the biceps femoris muscle of the chameleon. Intocostin was injected locally into the biceps femoris muscle and 3 minutes later quinine sulfate was injected into the same location. Three minutes after the injection of the quinine sulfate locally, ammonium hydroxide was injected into the peritoneal cavity. The animal died in 2 minutes after injection of ammonium hydroxide in a state of violent spasm. One per cent of the end-plates had acute retention cysts which contained a substance that had strong affinity for gold chloride. These acute retention cysts were found either in the epilemmal (Fig. 73) or hypolemmal (Fig. 74) axons or they were found in both locations (Figs. 75 and 76). The morphologic accompaniment of these acute retention cysts which contained aurophilic substance was the diminution in the projection of the hypolemmal axons. The chemical block to the secretion of the granules by the hypolemmal axons together with excitation in the transmission of the nerve substance to the end-plate may be compared roughly to the production of a lake behind the dam erected in the course of a flowing river. This is experimental evidence that a liquid nerve substance is secreted normally from the motor end-plates into the muscle substance. Intocostin and quinine apparently form a dense precipitation-membrane, by astringent action, around the periphery of the naked hypolemmal axons. This impermeable precipitation-membrane would then inhibit the normal transference of the axonic substance into the secretion granules of Kühne. Where this mechanical block by chemical action has become adequate, the circumscribed dilatations of the hypolemmal axons appear to possess a thickened membrane around which there is a diminution or complete absence of the granules of Kühne (Figs. 74 and 76). In other locations of the same end-plates, where the block has not become complete, there are hypolemmal axons surrounded by granules of Kühne. The teasing technic of muscle fibers impregnated previously with gold chloride preserves the anatomic continuity of the epilemmal axon, hypolemmal axon, ramifications of the terminal axons, the granules of Kühne and the muscle striations. $\times 750$.



Carey Motion and Secretion of Motor End-Plates

PLATE 73

FIGS. 77 to 82. Pleomorphism of the epilemmal (epa.) and hypolemmal (hya.) axons of motor end-plates in the biceps femoris muscle of the chameleon. Intocostarin was injected locally into the biceps femoris muscle and 3 minutes later quinine sulfate was injected into the same location. Three minutes after the injection of the quinine sulfate locally, ammonium hydroxide was injected into the peritoneal cavity. The animal died in 2 minutes following injection of ammonium hydroxide in a state of violent spasm. One per cent of the end-plates had acute retention cysts which contained a substance that had strong affinity for gold chloride. These acute retention cysts were found either in the epilemmal (Figs. 80, 81 and 82) or hypolemmal axon or in both locations (Figs. 77, 78, 79, 80, 81 and 82). The morphologic accompaniment of these acute retention cysts which contained aurophilic substance was the diminution in the projection of the hypolemmal axons. These acute retention cysts are surrounded by a definite, circumscribed membrane which apparently has been thickened and precipitated by the chemical actions of intocostarin and quinine. There are no secretion granules of Kühne surrounding these cystic dilatations of the hypolemmal axon. Apparently an effective block has been produced to the secretion of Kühne's granules around the retention cysts which contain a substance having a very strong affinity for gold chloride. $\times 750$.

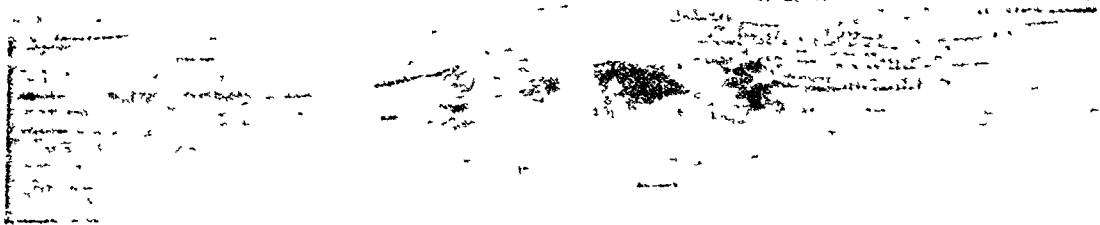


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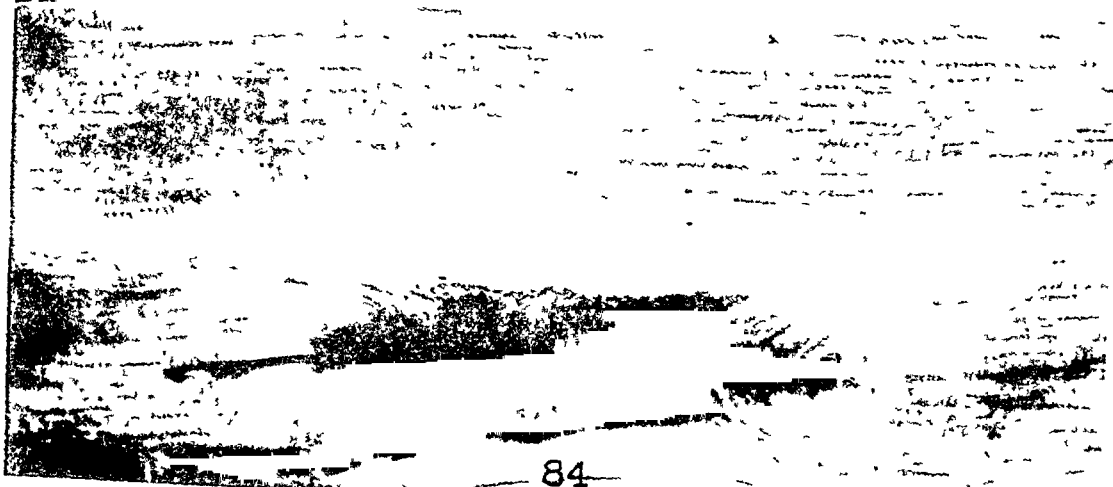
Motion and Secretion of Motor End-Plates

PLATE 74

FIGS. 83 and 84. Sudden conduction of masses of nerve substance into the motor end-plates of the biceps femoris muscle of the chameleon by the action of tetraethyl lead injected into the peritoneal cavity. This acute conduction of nerve substance into the end-plate results in a complete distortion by the explosive action of this substance which disrupts the end-plates. There are radiations of gold-staining substance extending from the terminals of the distorted end-plates as though a violent explosion had destroyed the normal morphology of the end-plate. There is an abnormal accumulation of gold-staining substance in the disrupted plates. This likewise applies to the morphology of the cross-striated muscle substance in close proximity to these end-plates. $\times 300$.



83



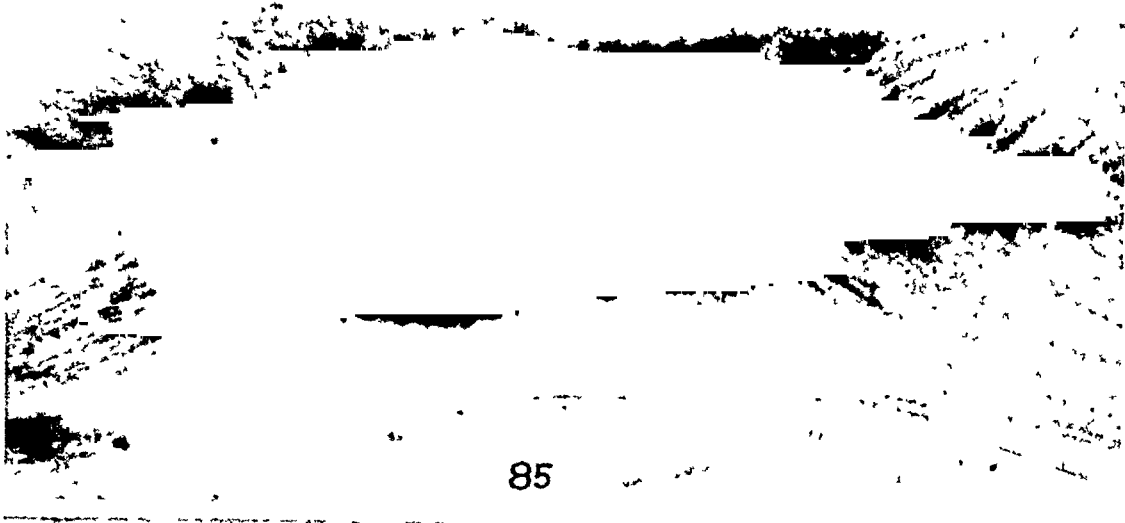
84

Carey

Motion and Secretion of Motor End-Plates

PLATE 75

FIGS. 85 to 87. Motor end-plates in the biceps femoris muscle of the chameleon disrupted by the explosive chemical action of tetraethyl lead injected into the peritoneal cavity. There is a massive conduction of an increased amount of gold-staining substance into the motor end-plates, which massive conduction appears to have a violent, explosive effect by destroying the normal morphology of the end-plate. Radiations of gold-staining substance extend from the terminals of the destroyed end-plate. These radiations appear to be the effect of explosive violence which radiates out into the striated muscle substance and destroys the normal morphology of the cross striations in many places. The chemical action of tetraethyl lead apparently delivers suddenly abnormal amounts of the gold-staining axonal substance to the end-plate. This super-normal transmission of nerve substance destroys the myoneural junction with explosive violence and shatters the normal morphology by a real intramuscular chemical explosion of some of the motor end-plates. $\times 750$.



Carey Motion and Secretion of Motor End-Plates

PULMONARY MUCOUS EPITHELIAL HYPERPLASIA (PULMONARY ADENOMATOSIS)

A REPORT OF TWO CASES *

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In the first article relative to pulmonary mucous epithelial hyperplasia (pulmonary adenomatosis) in man, Helly¹ remarked that it was a rare tumor which he described "to arouse interest because only the study of many similar cases will clear up the subject." In the past 4 years interest has again been aroused in this condition by the publication of reports of three similar cases by Bonne,² Richardson³ and Sims.⁴ In Sims' article, a most thorough and exhaustive review of the literature, the similarity of this condition to one seen in sheep was emphasized. This latter disease, variously known as jagsiekte, epizootic adenomatosis, and pulmonary adenomatosis, has a wide incidence in the sheep herds in South Africa, Iceland, Montana and Germany. Six human cases in all have been previously described.¹⁻⁶

REPORT OF CASES

Case 1

Clinical Course. The first case was that of a white male, 62 years of age, who was admitted to the Essex County Sanatorium on August 8, 1941, with a cough of 8 months' duration. About 1 month before developing his cough he began to notice undue fatigue. His cough became worse and during the winter of 1940-41 productive of 10 to 20 ounces of white, sticky, foamy sputum in 24 hours. In January, 1941, he began to notice loss of weight and strength. In March there was dyspnea on slight exertion. He consulted a doctor in June who sent him to the Sanatorium's Outpatient Department, after he had had to quit work. On July 20th he was advised to enter the Sanatorium.

His past history was negative except for "pleurisy" in the fall of 1940. One of his brothers was thought to have had tuberculosis in 1920.

He was a fairly well developed and well nourished man (height, 67¼ inches; weight, 145 pounds) who did not appear in acute distress. His temperature, pulse, respiration and blood pressure were not remarkable. Chest expansion was limited. There was no dullness to percussion and many coarse moist râles were heard over the chest on auscultation. Otherwise physical examination was negative.

The hemoglobin content of the patient's blood was 80 per cent (Sahli). The white cell count was 11,400 with 74 per cent polymorphonuclear leukocytes, 24 per cent lymphocytes and 2 per cent large monocytes. There seemed to be a marked increase in platelets in the smear. The sedimentation rate was not increased. The urine was not remarkable. The sputum showed no tubercle bacilli on three examinations and but few leukocytes.

* Received for publication, July 1, 1943.

Roentgenograms of the chest taken on July 24th and August 9th showed essentially similar findings (Fig. 1). They were read as follows: "There are diffuse mottled flocculent areas from apex to third rib on the right. There is a homogeneous shadow from the third to the fifth rib. This shadow covers the entire base, but is lighter toward the costophrenic angle. There is heavy infiltration on the left from the apex to the third rib. Below, the entire lung is obscured by a homogeneous shadow." This was interpreted as possibly a fungus infection or a tumor. On August 18th a Bucky plate was taken (Fig. 2) which did not reveal anything of further interest.

The patient's von Pirquet tuberculin test was very weakly positive. Bronchoscopy on August 21st revealed a profuse mucoid secretion in both major bronchi which apparently interfered with respiration. No localized lesion was found in the tracheobronchial tree. The secretion was interpreted as consistent with cardiac decompensation.

Three days prior to his death on the 19th hospital day the patient became markedly dyspneic and cyanotic and was placed in an oxygen tent with temporary relief. He became febrile at this time and remained so until his death on August 27th.

Autopsy Findings

At autopsy, 2 hours post-mortem, the body was that of a moderately well developed, somewhat thin white male. The dome of the diaphragm was at the 7th rib on the right and the 7th intercostal space on the left. There were numerous fresh fibrinous adhesions in both the right and left pleural cavities. The only other significantly abnormal findings were confined to the lungs.

The left lung weighed an estimated 900 gm. It was firm and consolidated. The pleura was covered with a thin coat of yellow fibrin. On section the upper lobe was gray-white with a glairy, mucoid appearance. On scraping with the section knife, a large amount of tenacious mucus was expressed from the cut surface. At the apex there was a gray-red, more granular zone, with several small areas of cavitation varying from 0.4 to 1.5 cm in diameter. The lower lobe presented the same glairy, mucoid appearance. The bronchi contained moderate amounts of mucoid material, and their mucosae were reddened and edematous. The pulmonary vessels were negative. The right lung weighed an estimated 850 gm. It showed almost complete consolidation of the entire lung with a few small peripheral zones of aeration. On section, it presented the same picture as the left lower lobe.

Microscopically, the lungs showed the only pathological changes of note. The alveoli were largely dilated. A few contained mucus, but for the most part they were filled with leukocytes and blood. The majority of the alveolar walls taken at random from various lobes of the lungs were covered by a simple columnar epithelium. In a few areas this epithelium showed a transition to a cuboidal type, but as a rule the change from the abnormal epithelium to the usual type was

abrupt, as if the alveoli were being invaded by the pathological cells. In some areas the columnar epithelium had formed small papillary processes.

The columnar cells were slender with pale cytoplasm and basally located nuclei. The cells were somewhat larger than the usual epithelial cells of the bronchial mucosa and were not ciliated. The nuclei occupied approximately one-sixth of the length of the cells and were for the most part round or oval with a pale network of chromatin. No mitoses were noted.

The alveolar walls were minimally thickened and contained an unusual number of lymphocytes. No abnormal epithelial cells were found in the lymphoid tissues of the lung. In one area there was marked increase in the fibrous connective tissue with loss of the usual architecture. The columnar epithelium in this area was arranged in small acinus-like structures.

The bronchiolar epithelium and that of the alveolar ducts did not seem to be affected by this process.

Case 2

Clinical Course. The second case was that of a white female, 79 years of age, who was admitted to the Boston City Hospital on the Fifth Medical Service on October 23, 1942. On a previous admission to the hospital in 1932 a diagnosis of primary anemia had been established. Since then she had had occasional injections of liver extract and had taken three liver capsules daily until about a month before her last admission. In the 2 months prior to admission the patient lost 20 pounds in weight. For 2 months she had severe anorexia and a dull pain in her epigastrium. She became pale and faintly yellow. She was bedridden for 1 month before entry. Her family history and past history were otherwise negative.

She was a markedly emaciated small woman (height, 56½ inches; weight at autopsy, 70 pounds) with lemon-tinted skin. Her tongue was pale and smooth with atrophic papillae. Her neck veins were distended, and her heart seemed to be enlarged to the left with systolic apical and aortic murmurs. Her lungs were clear to percussion and auscultation and no râles were heard. Her liver was just palpable. Her knee, ankle and abdominal reflexes could not be obtained.

Her red cell count was 860,000 with 4.5 gm. of hemoglobin per 100 cc. of blood. Her white cell count was 3,800 with 54 per cent neutrophilic leukocytes, 43 per cent lymphocytes, 1 per cent eosinophilic leukocytes, and 2 per cent basophilic leukocytes. A smear showed anisocytosis, hyperchromia, polychromasia, and basophilic stippling of the red cells. The platelets seemed to be decreased. The hematocrit reading was 12 mm. There were 1.2 per cent of reticulocytes. Examination of the urine and a Hinton test of the blood were negative. Her sputum was not examined. A roentgenogram taken on November 8th (Fig. 3) was interpreted as showing consolidation at the left base with focal pneumonia or encapsulated fluid in the region of the right middle lobe.

The patient was given three transfusions of 500 cc. each of citrated whole blood during the first week of her hospital stay. She also received daily injections of liver extract. Her reticulocyte count reached its maximum level of 13 per cent on the

5th hospital day. On the 14th hospital day the red cell count had increased to its maximum of 4,000,000. At this time her hematocrit reading was 42 mm.

On the 8th hospital day the patient developed a cough and consolidation of the left lower lobe was diagnosed. Signs and symptoms indicated increased infection, and the white blood cell count rose to 10,000. Three days prior to death the patient was stuporous and failing rapidly. Chemotherapy was not used. The patient died on the 27th hospital day.

Autopsy Findings

At autopsy, 7 hours post-mortem, the body was that of a well developed, emaciated white woman. Her abdominal panniculus was less than 0.5 cm. in thickness. There were about 300 cc. of clear yellow fluid in the right pleural cavity. The posterior portion of the left pleural cavity was completely obliterated by firm fibrous adhesions so that the lower lobe had to be cut away from the parietal pleura by sharp dissection. The heart weighed 280 gm. and was not remarkable. The gastric mucosa was markedly atrophic. Many diverticula were found in the sigmoid portion of the colon. These showed no surrounding reaction. The liver was small, weighing but 700 gm. It was somewhat browner than usual and cut with slightly increased resistance. It was not otherwise remarkable. The gallbladder contained a number of faceted stones, but its mucosa did not appear abnormal. The spleen weighed 120 gm. and was not remarkable. The kidneys weighed 190 gm. They showed a coarsely granular surface and, on section, a moderately thinned cortex which was well demarcated from the medulla. The bladder was dilated and contained 750 cc. of clear amber urine. The genital organs were markedly atrophic. There was moderate atheromatosis of the abdominal portion of the aorta. The lumbar, sternal, costal and femoral bone marrow was markedly soft, dark red and gelatinous.

The most significant findings were those in the lungs. The right weighed 700 gm. The lower and middle lobes were consolidated and showed no crepitation. The upper lobe was subcrepitant. On section the lower and middle lobes revealed a smooth cut surface which was dark red peripherally and gray in the central portions. The lower portion of the upper lobe was similar to the peripheral portion of the lower lobe. The rest of the upper lobe was dark red and yielded serosanguinous fluid on pressure. The consolidated portions of the lung yielded sanguinopurulent scrapings.

While the left lung was being removed, the upper and lower lobes were inadvertently separated. The lung weighed 420 gm. The lower lobe was ovoid and measured 8 by 6 by 4 cm. On section it was firm and pale gray, and had a gelatinous pink-gray, mulberry-like tumor process involving the central portion of the lobe. The bronchi were

small but unusually prominent. The left upper lobe resembled the right upper lobe except that the lingula contained several small spherical areas resembling the pink-gray gelatinous area described in the lower lobe. The trachea and bronchi of both lungs were congested and contained a moderate amount of mucoid secretion. The pulmonary vessels were not remarkable.

Culture of the heart's blood and of the right lower lobe revealed *Diplococcus pneumoniae*, type VIII. Culture of the left lower lobe revealed *D. pneumoniae*, type VIII, and hemolytic *Staphylococcus aureus*. A Ziehl-Neelsen stain of the lung revealed no acid-fast organisms.

On microscopical examination, the arterioles in most of the viscera showed a moderate amount of hyaline change. The perinuclear yellow pigment of the heart muscle cells was somewhat more prominent than usual. There were no changes of note in the liver. The kidneys showed occasional fibrosed glomeruli. No parietal (eosinophilic) cells could be found in the mucosa of the stomach. The bone marrow showed moderately active hematopoiesis as is seen in adequately treated primary anemias.

The lung sections showed the microscopical changes which were of interest. The majority of the sections showed merely a confluent bronchopneumonia. The unusual findings were confined to the left lower lobe, to the lingula of the left upper lobe, and to a small portion of the right upper lobe.

In scattered nodules in the upper lobes, the alveoli were lined with columnar epithelium. The epithelial cells were similar to those of the first case except that they were proportionately higher so that they almost obliterated the lumen of the alveoli in some areas. The surrounding alveoli were filled with mucoid secretion and desquamated cells, apparently of epithelial origin. Aniline blue stains revealed that the cells as well were filled with mucus. Cuboidal epithelium was not seen and no bronchioles could be identified with certainty. There was no invasion of the lymphoid tissues of the lungs.

The left lower lobe had been almost completely replaced by hyalinized collagenous fibrous tissue. There were islands of abnormal epithelium lining spaces as large as bronchioles. Areas of alveoli lined with abnormal epithelium also were seen. The bronchi and bronchioles appeared to be unaffected.

Elastic tissue stains revealed no change and aniline blue stains revealed a slight increase in the fibrous tissue of the alveolar septa in the areas involved by the process in question.

DISCUSSION

The pathological picture as described in the two cases reported is essentially similar to that described in earlier articles. In both cases the disease picture was somewhat obscured by severe superimposed bacterial infections. The gross picture in this condition is very similar to that seen in Friedlander's pneumonia. Even microscopically the condition might easily be overlooked in cases with severe bacterial infections, so that it is not impossible that other cases of this nature have not been noticed in the past.

In the first case the clinical course can readily be correlated with the pathological findings, as in Helly's¹ case. The clinical course in both was similar to that of pulmonary tuberculosis. In the second case, however, the mucous epithelial hyperplasia was an incidental finding at autopsy which was not recognized until the microscopical sections were seen. The roentgenographic pictures in both cases were similar and an infectious process or a tumor was suspected in each.

The duration of the disease in these cases is problematical. In both of them there were areas of marked fibrosis in the lungs which seemed to indicate a protracted, chronic infection rather than an acute or neoplastic process. The most acute case in the literature, the second described by Oberndorfer,⁶ was accompanied by an acute hemorrhagic pneumonitis of short duration in a 21-year-old male. In sheep, on the other hand, the course is not as acute. Sheep die, as a rule, within a few months after the infection is first noted, although some may live for more than a year.⁷

In the discussions of this and similar diseases in the literature, emphasis has been placed on the importance of such lesions in the consideration of the genesis of carcinomas of the lung. There are several phases of this problem upon which it is worth while to speculate. In the first place, where do these proliferating cells arise? Helly¹ favored the epithelium of the alveolar ducts for several reasons: (1) because the cells were nonciliated in contrast to those of the bronchioles; (2) because the cells could be seen extending from the alveoli to the bronchiolar mucosa but no farther; and (3) because there was a sudden transition from the abnormal cells to the usual alveolar lining. Oberndorfer,⁶ on the other hand, was of the opinion that in his case, at least, the tumor arose from the lining cells of the alveoli which he believed have an epithelial origin. He felt that he could demonstrate gradual transitions between pathological cells and the usual alveolar lining cells.

In our opinion, a definite decision is difficult to arrive at; but because of their apparently peripheral and multicentric origin, it seems not unlikely that the abnormal cells arise from the alveolar lining cells (also the opinion of Dr. J. L. Bremer*), and provide further evidence for the epithelial nature of those cells. The changes are of a hyperplastic nature and there is also some metaplasia; for, although the cells are not ciliated, they are columnar and produce large quantities of mucus. In support of our contention, we note that this picture in no way resembles that seen in pulmonary adenomas of which the structure has been quite definitely established in recent years.⁸ In that condition the hyperplastic nodules have ill-defined borders and are not encapsulated. They have no stroma other than that of the alveolar walls. Their cells frequently fail to fill more than a small portion of an alveolus. Their exact site of origin is somewhat more problematical.

It seems to us that Oberndorfer's⁶ ideas are quite in accord with the picture presented in cases of the type which we have described. Helly's¹ ideas cannot be dismissed readily, however. In one of our cases intact alveolar duct epithelium was seen in several areas in which the alveoli were completely lined with abnormal cells. Thus in this case the microscopical picture is at variance with Helly's opinion. In sheep there are peculiar mucous glands in the walls of the respiratory bronchioles, and many authors believe that it is there that the proliferation starts. From the nature of these cells in man it is not impossible that they may arise from the occasional mucous goblet cells which occur in the mucosa of the bronchioles.

Are these tumor masses of infectious origin? There has been but one case in the literature in which the nature of this disease has been suspected at the autopsy table and confirmed by frozen section.³ In that case attempts were made to produce a similar condition in experimental animals by the usual methods with no success. That the microscopically similar disease in sheep is of an infectious nature is undoubtedly true, but transmission of the disease from sheep to sheep or to any other laboratory animal has been almost universally unsuccessful. However, the disease has been proved to be infectious in nature, as is evident from a study of the epidemic which occurred in Iceland.⁹ It seems that a virus is the most tenable cause for the hyperplasia, since no bacterial species has been recovered with any regularity from affected sheep.

A number of human cases with a more or less similar microscopical

* Personal communication.

picture have been described in which, however, metastases have been found—usually to the regional lymph nodes and occasionally to bone marrow and the brain. References to 10 or 11 such cases have come to our attention.¹⁰⁻¹⁷ The published descriptions of all but 3 of these¹⁵⁻¹⁷ have been examined by us. They all present a somewhat similar picture to the apparently nonmalignant cases described by other authors, although the production of mucus is not a constant finding in the malignant cases as in the nonmalignant condition.

Thus in respect to these few instances, on a histological basis and by analogy, it can be said that these carcinomas may be of an infectious origin. Aynaud is said to have seen metastases in one case of jagsiekte in a sheep (cited by Dungal⁹). However, in our opinion these tumors have but little significance in the consideration of the origin of carcinomas of the lung in general, because the large majority of pulmonary carcinomas obviously do not arise in such a manner but are bronchiogenic.

In a recent review of the case reports of such carcinomas, Neuburger and Geever¹⁸ agreed that this type of tumor was rare, with an incidence of less than 5 per cent of all carcinomas of the lungs. They feel, as we do, that mucous epithelial hyperplasia may not be as rare as the number of reports in the literature would indicate.

SUMMARY

Two cases of pulmonary mucous epithelial hyperplasia (pulmonary adenomatosis) are described. After reviewing the available literature, the possibility of a viral etiology is considered. While a definite decision cannot be made, it seems probable that the abnormal cells arise from the alveolar lining. Origin from the goblet cells of bronchiolar mucosa cannot be excluded. This condition is of but little significance in a consideration of the genesis of pulmonary carcinoma in general.

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[Illustrations follow]

DESCRIPTION OF PLATES

PLATE 76

FIG. 1. Case 1. Roentgenogram taken on July 24, 1941.

FIG. 2. Case 1. Bucky plate roentgenogram taken on August 18, 1941.



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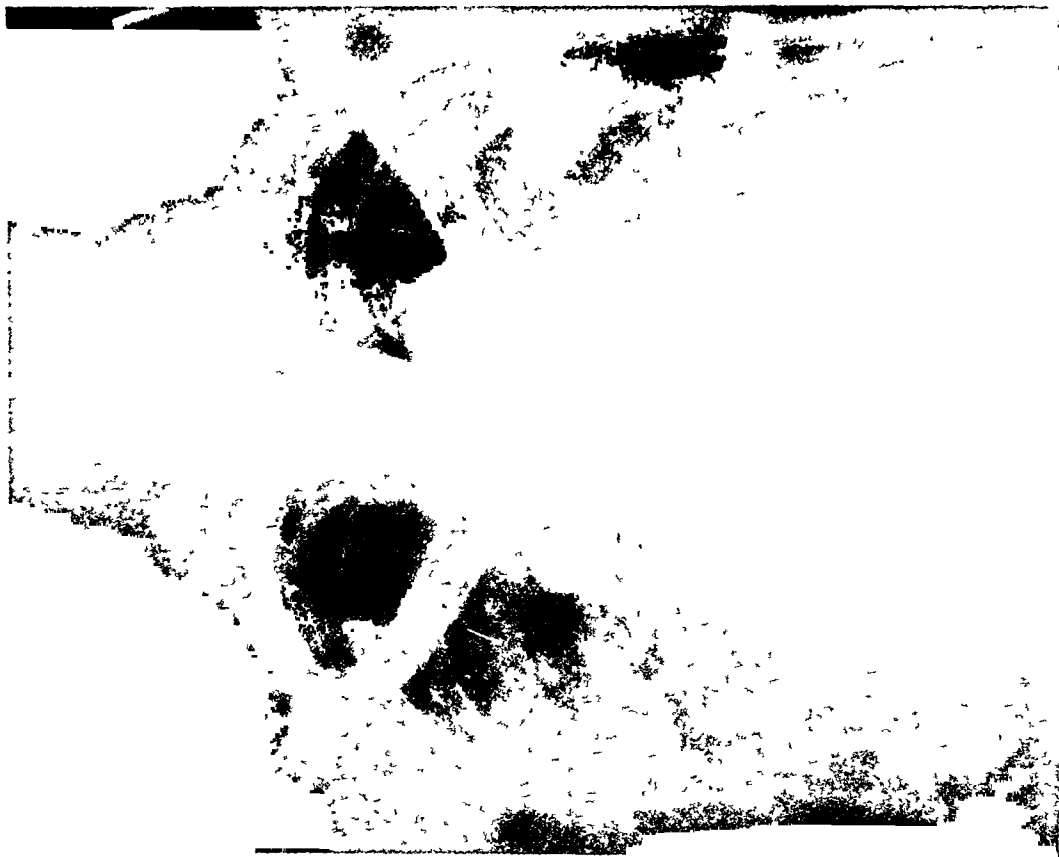
PLATE 77

FIG. 3. Case 2. Portable roentgenogram taken on November 18, 1942.

FIG. 4. Case 1. An uninvolved bronchiole with attached alveolar duct in an area with marked replacement of the usual alveolar lining by typical columnar, nonciliated epithelial cells. Hematoxylin and eosin stain. $\times 175$.



4



3

Taft and Nickerson

Pulmonary Mucous Epithelial Hyperplasia

PLATE 78

FIG. 5. Case 1. A small cluster of abnormally lined alveoli in the midst of uninvolved alveoli. Hematoxylin and eosin stain. $\times 175$.

FIG. 6. Case 2. A small collection of abnormal alveoli with the surrounding spaces filled with large quantities of intensely stained mucus which contains desquamated cells. Phloxine and methylene blue stain. $\times 175$.

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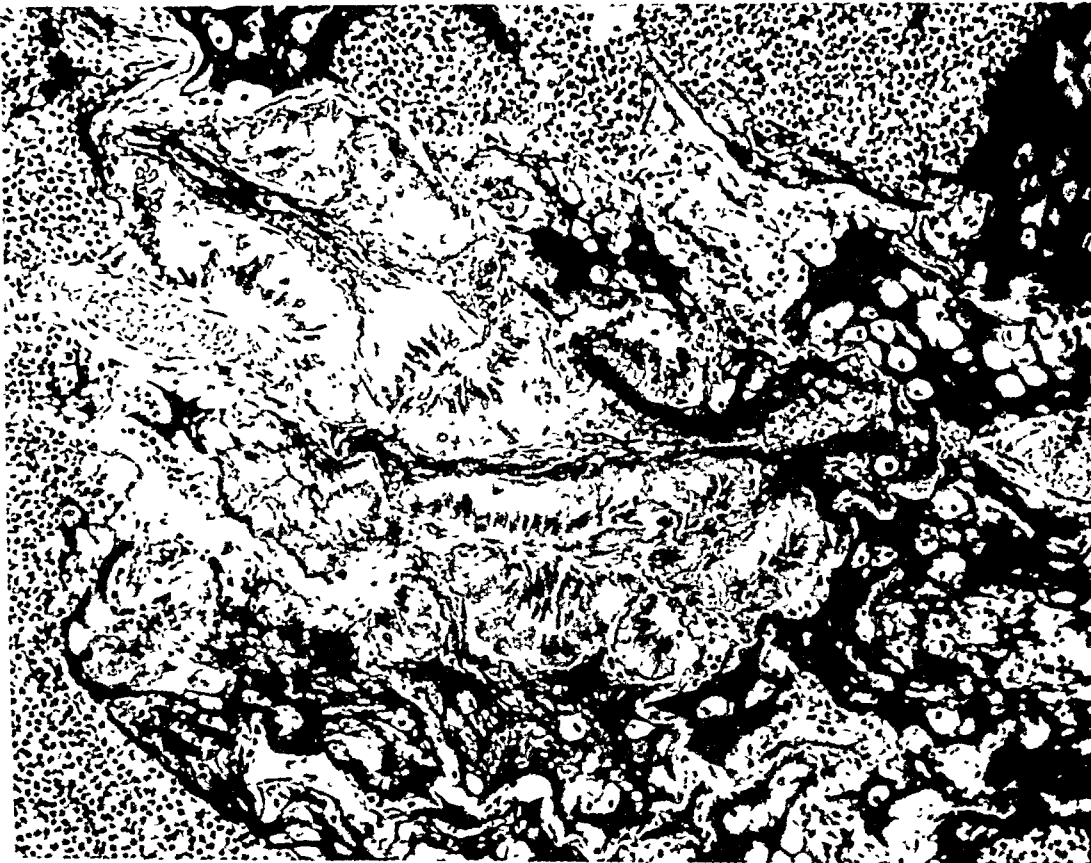
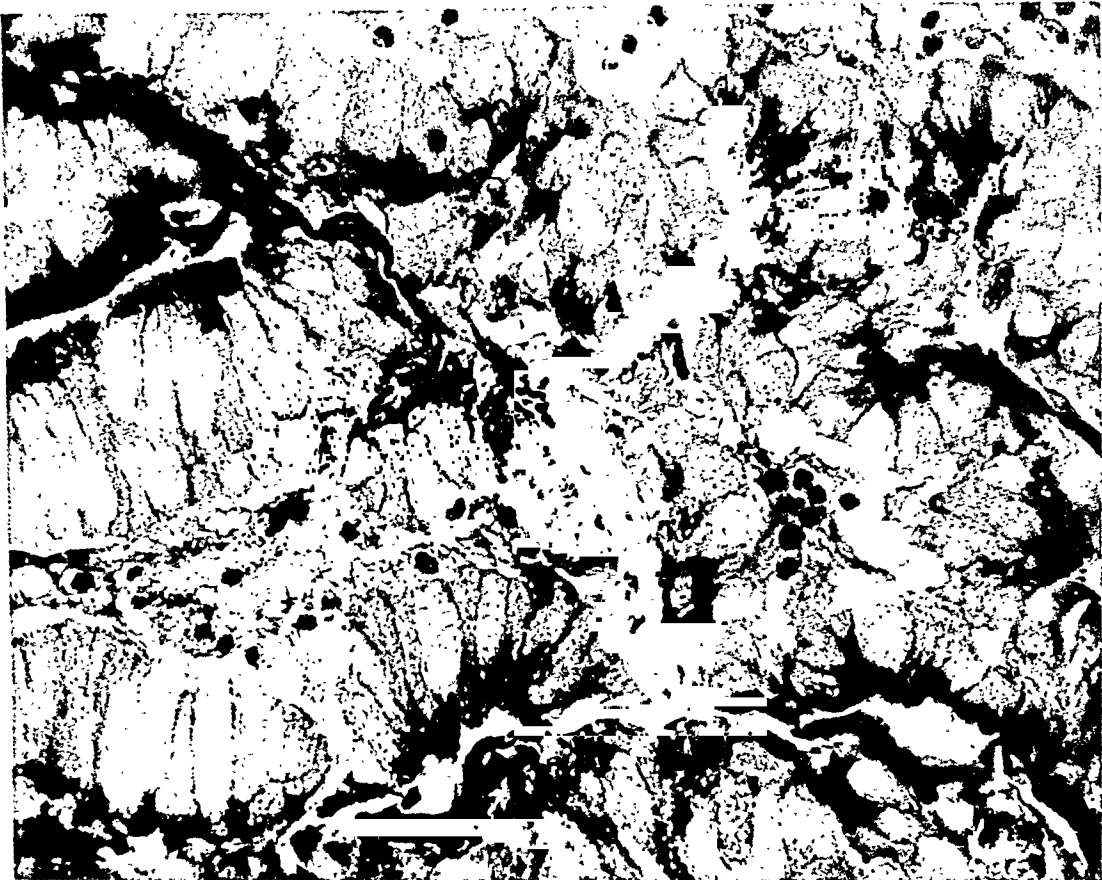


PLATE 79

FIG. 7. Case 2. Detail of the epithelial cells and alveolar walls to show that the latter are not involved or markedly changed by the hyperplastic process. Iron hematoxylin stain and Lee-Brown's modification of Mallory's aniline blue stain. $\times 390$.

FIG. 8. Case 2. Photomicrograph of the left lower lobe, showing the marked fibrosis which the lobe has undergone. There is a central space lined with abnormal epithelium which shows moderately large papillary processes. Phloxine and methylene blue stain. $\times 175$.

7



8



NEURILEMOMAS IN A FAMILY OF BROOK TROUT *

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The tumors described in this article were discovered during some bacteriological and pathological studies of trout which were being made to determine the cause of mild losses in the brood stock of a hatchery. Sections were made from all of the internal organs which were cultured for bacteria. Examination of these sections disclosed the presence of a characteristic tumor affecting the peripheral nervous system.

Tumors in fish are not uncommon and nearly every type of tumor reported in mammals occurs in fish. A report of a neoplasm of the peripheral nerves in trout, however, was not found in the literature.

MATERIAL

The material for this study was obtained from 41 trout. All but 7 of these were supplied by a single hatchery. The distribution of the species studied and the source of supply is indicated in Table 1.

The oldest trout obtained from hatchery no. 1 were known to have been inbred for at least 2 generations and the youngest fish were inbred from 3 to 4 generations. The extent of the inbreeding in the brood stock before it was placed in this hatchery is not known.

All tissues were fixed in formaldehyde, embedded in paraffin and stained with hematoxylin and eosin. Representative sections were stained by Masson's trichrome and Mallory's acid fuchsin technics. Gram's stain and an acid-fast stain were used in an attempt to demonstrate bacteria in a few selected sections. Because of the difficulty involved in handling the tiny organs of the young fish, only cross sections

TABLE I
Source of Material for Study

Species	Source and number of trout		
	Hatchery no. 1	Hatchery no. 2	Natural
Brook trout (<i>Salvelinus fontinalis</i>)	23	2	0
Brown trout (<i>Salmo trutta fario</i>)	7	1	0
Rainbow trout (<i>Salmo gairdnerii irideus</i>)	4	1	0
Lake trout (<i>Cristivomer namaycush</i>)	0	1	2

* Received for publication, June 7, 1943.

through the intestine with the adjoining pancreas and through the kidneys were made. Cross sections of the entire fish were made in studies of 1 and 2-month-old trout.

INCIDENCE

All of the brook trout examined were found to be affected with neurilemmomas. This group consisted of 25 trout obtained from two hatcheries. The severity of the affliction was found to be directly related to age, the organs of the oldest fish being most extensively involved. Both sexes were equally affected.

Studies were attempted on embryos and fry but the methods used in fixation made the yolk material too hard to section. Fingerlings which had just begun to feed were studied, however, and showed mild involvement of the nerves at an age of 1 month. Material was collected from July to January but no seasonal variation was evident. Two mature brook trout from hatchery no. 2 were found to have these tumors but to a lesser degree than trout of the same age from hatchery no. 1.

Only one trout of a different species was found to be affected with neurilemmomas. This was a 2-year-old brown trout taken from hatchery no. 1. A single nerve trunk in this fish was found to be tumorous. All other brown trout were found to be negative. No rainbow or lake trout were affected.

PATHOLOGY

The pathological changes in this disease were principally microscopical. In some specimens moderate enlargement of the nerve trunks supplying the stomach, intestine and kidneys was seen. There were no other lesions except small surface ulcers in some specimens. There was no evidence to indicate any relationship between these ulcers and the tumors of nerves.

The tumors studied were uniform and characteristic in their structure and not unlike the neurilemmomas described by Bailey and Herrmann.¹ All lesions were arranged more or less in whorls. The outermost portion consisted of a band of collagenous tissue of variable thickness surrounding concentric layers of fibrous tissue. These two tissue arrangements were constant. The centers of the lesions, however, were variable.

The most uniform lesions were made up of collagenous and fibrous concentric rings surrounding a group of cells. These cells were for the most part polyhedral with a variable amount of eosinophilic and finely

granular cytoplasm. The nuclear chromatin was scattered in many large sharply stained granules. This type of lesion is illustrated in Figure 4.

Other tumors consisted of laminated layers surrounding a mass of hyaline material (Fig. 3). Some of these lesions were calcified as illustrated in Figures 2 and 5. Large giant cells (Fig. 6) and brownish pigment were observed in some of the neurilemmatous nerve trunks.

The most extensive lesions occurred in the mesentery and pancreas. Many whorled masses surrounded and connected by collagen were observed. Figure 3 shows a representative area from a cross section of a tumorous nerve running through the mesentery in a 3-year-old brook trout. This nerve trunk was approximately 0.5 cm. in diameter. In fingerlings and yearlings, the lesions were generally limited to a few nerve trunks. Tumors in the very young fish, less than 2 months old, were limited to one or two foci in a cross section of the whole fish. The submucous and myenteric plexuses of the intestine were occasionally affected.

Involvement of the nerves in the kidneys was sometimes extensive. In one 4-year-old brook trout more than half of the kidney tissue in the section had been replaced by the affected nerve trunks. Renal involvement seemed to increase with age.

Nerves to other organs were found to be involved but not with the regularity of those in the mesentery and kidneys. Lesions were found occasionally in the nerves to the heart, testicle and spleen. In no case was the liver found to be involved.

In a limited study of the sensory nerves of the affected brook trout, all were found to be normal. The large lateral subcutaneous nerve was not found to be affected.

Inclusion bodies were not observed in any of the tissues. Many of the sections were examined with a micropolarizer but failed to show evidence of crystals. Representative tissue sections were stained with Gram's and acid-fast stains but no evidence of bacteria was found in any of the sections. Attempts to culture microorganisms from the liver, heart and kidneys of many of the fish were unsuccessful.

DISCUSSION

The tumors in trout arose from the perineurium and endoneurium. Following the terminology suggested by Stout,² these tumors are called neurilemmomas. There is considerable controversy as to the origin of tumors of this type but from the observations made in this study, the

connective tissue-like elements in and around the nerve fibers were primarily involved.

Tumors of the peripheral nerves have been reported in various mammals but the incidence has been low. This is in contrast to the very high incidence found in this family of brook trout.

The fact that every brook trout examined, regardless of age, was affected with a neurilemoma suggested that the condition is hereditary. Only one fish of related species was found to be affected. This trout was taken from the same hatchery as the affected brook trout. It is possible that cross-insemination may have occurred.

Studies of the affected nerves in brook trout indicated that the autonomic nerves were primarily involved. That both the sympathetic and parasympathetic nerves were affected was shown by involvement of the submucous and myenteric plexuses of the intestine. Nerves to the mesentery, heart and kidneys were also involved.

SUMMARY

Twenty-five brook trout (*Salvelinus fontinalis*) were found to be 100 per cent affected with neurilemmas. All but 2 of these trout were obtained from a single hatchery. Only 1 of 16 fish of three other species was found to be affected. The high incidence in brook trout of all ages in this hatchery suggested that the condition may be hereditary. The autonomic nervous system was found to be primarily involved.

We wish to thank A. V. Tunison of the Cortland, N. Y., Experimental Hatchery for supplying the material for study and for information relating to trout.

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DESCRIPTION OF PLATES

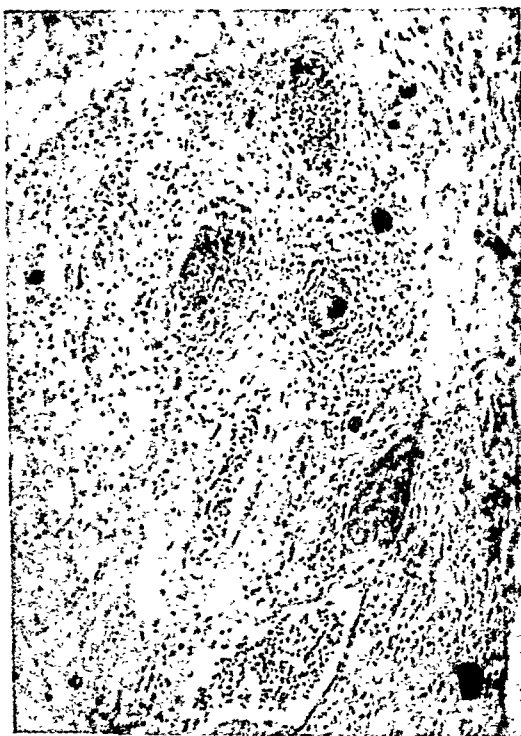
PLATE 80

- FIG. 1. Photograph of the stomach of a 3-year-old brook trout with an enlarged vagus nerve shown underneath the window cut in the organ.
- FIG. 2. Section from the vagus nerve shown in Figure 1. Whorls and calcified whorls are shown. Hematoxylin and eosin stain.
- FIG. 3. Section of a mesenteric nerve from a 3-year-old brook trout. Masson's trichrome stain.
- FIG. 4. Enlargement of an area in Figure 3 showing polyhedral cells with darkly stained chromatin granules in the nuclei.

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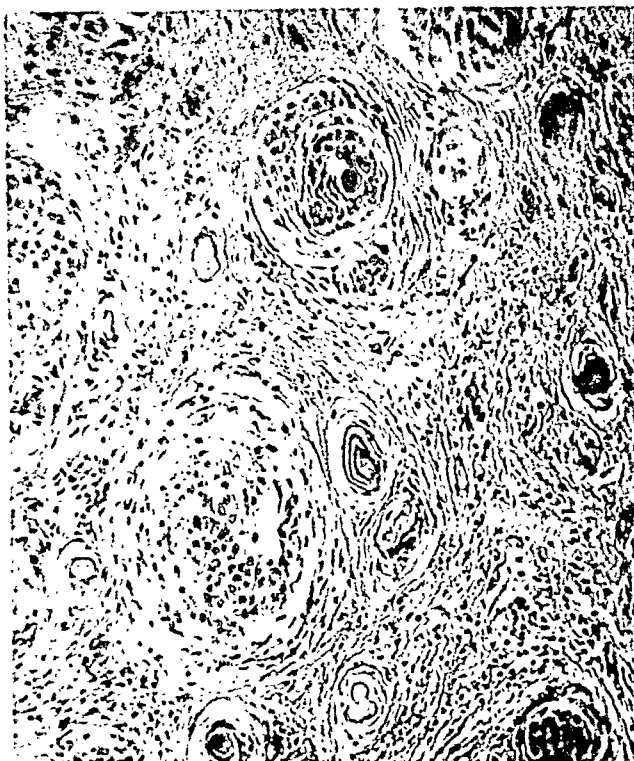


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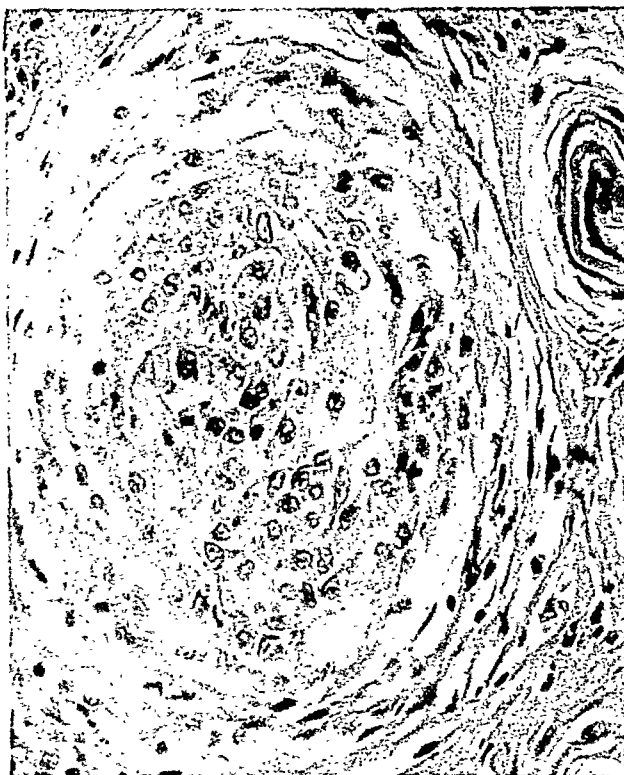


Young and Olafson

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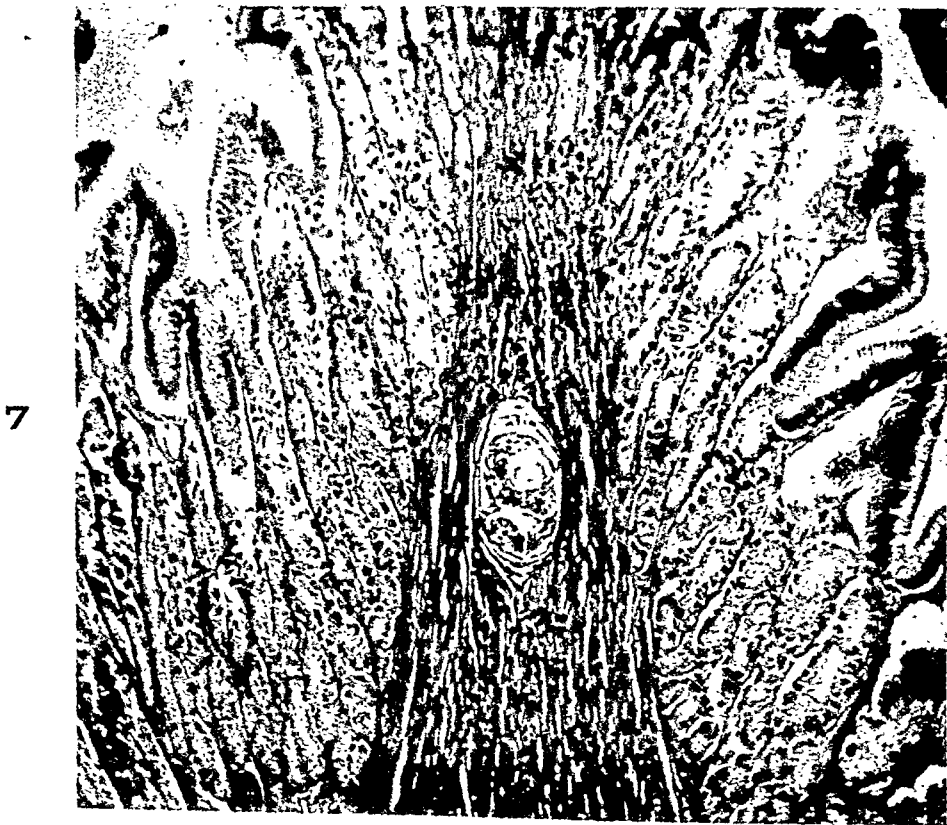
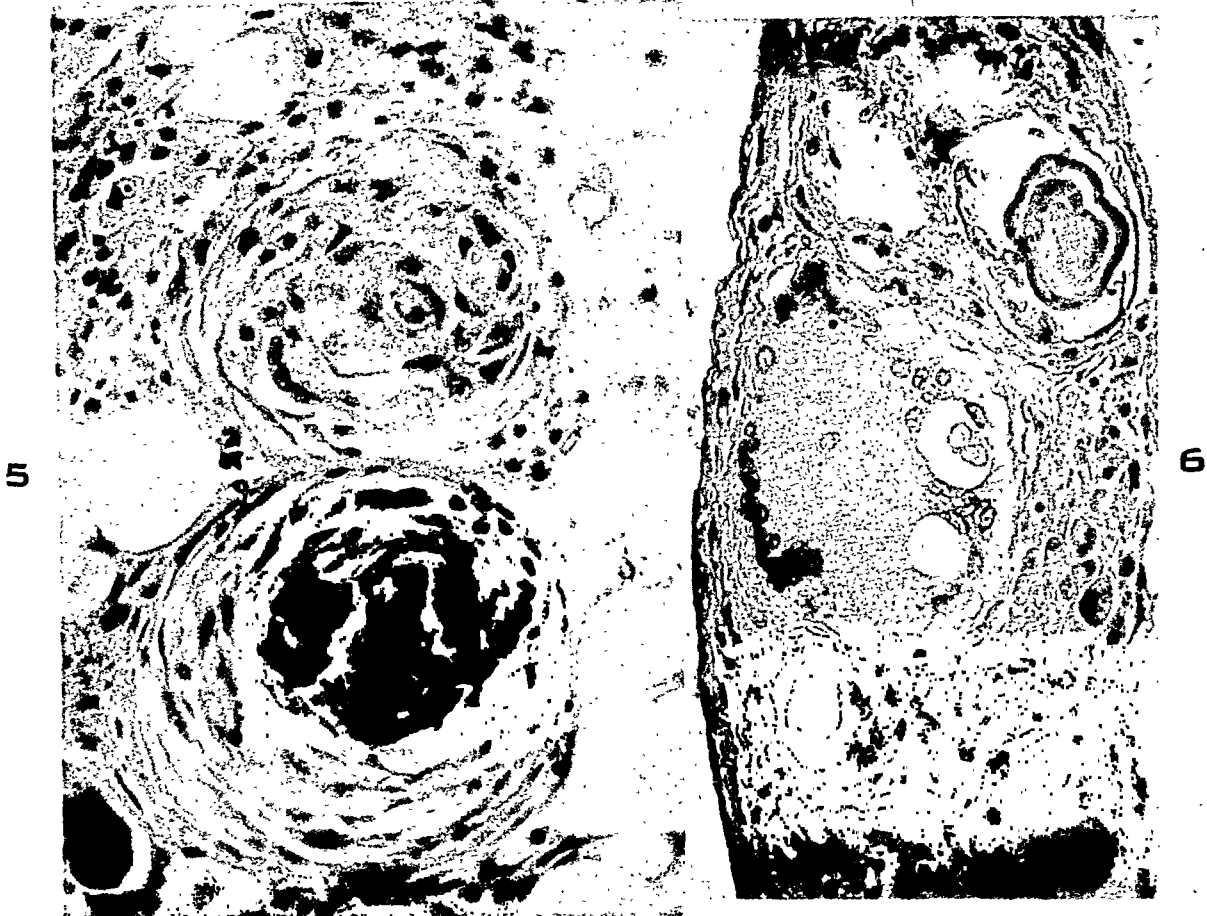
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Neurilemmomas in Brook Trout

PLATE 81

- FIG. 5. Section of a nerve from the mesentery of a yearling brook trout showing a calcified whorl in the lower portion of the photomicrograph. A cross section of an axon is evident in the upper left-hand corner. Hematoxylin and eosin stain.
- FIG. 6. Section of a cardiac nerve in a 2-year-old trout. A typical giant cell is shown. Hematoxylin and eosin stain.
- FIG. 7. Section of the intestine in a 3-year-old brook trout with involvement of the submucous plexus. Masson's trichrome stain.



ADENOMA OF THE BOVINE BLADDER *

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Adenoma of the bladder is a rare form of neoplastic disease, and only isolated cases have been published.

Feldman¹ reported a mucoid papillary adenoma associated with calculi in the bladder of a 4-year-old cow. The tumor consisted of a fleshy mass which was firmly attached to the mucosa of the body of the bladder by a rather broad base. Many small, yellowish, cystic foci were present throughout the tumor. Feldman² later mentioned another papillary adenoma of the urinary bladder of a bovine. The interior of the bladder was literally filled with hundreds of flattened, string-like prolongations of neoplastic tissue, many of which were approximately 5 cm. long. In Feldman's² book the adenoma of the bladder depicted (Fig. 135, p. 284) resembles the microscopic picture exhibited by the two adenomas herein described.

Feldman² mentioned Berg³ and Grips⁴ (quoted also by Fölger⁵) as reporting adenoma of the urinary bladder in the bovine. Ewing⁶ discussed the isolated reports of adenoma and adenocarcinoma of the bladder in human cases. Mihalovici⁷ noted adenomas of the bladder neck upon gross examination (human case). Makar and Urquhart⁸ described the gross and microscopic appearances of an adenoma of the bladder in a young man and Paschkis⁹ described five cases of adenoma of the bladder in man.

GROSS PATHOLOGY

In studies of bovine pyelonephritis¹⁰ abnormal growths in the bladder were found in two cases.

Case 1820. Guernsey, female, age 12 years. The bladder wall on palpation was thicker than normal. Many firm nodules were detected through the wall. On section the mucosa was markedly congested and showed some hemorrhage. The nodules were pedunculated growths extending from the bladder wall into the lumen (Fig. 1). Except for one area measuring 10 by 10 cm., the mucosa was in irregular folds. The abnormal growths cut with increased resistance and showed an arborescent pattern.

Case 6270. Guernsey, female, age 10 years. The gross appearance of the bladder was similar to that of case 1820 except that there were fewer pedunculated growths.

* Published with the permission of the Director of the Michigan Agricultural Experiment Station as journal article no. 650, new series.

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The neoplastic tissues were fixed in Zenker's fluid and stained with hematoxylin and eosin. Gram-Weigert stains for bacteria were also prepared.

HISTOPATHOLOGY

Microscopic examination of the nodules in the bladder revealed a neoplasm with the characteristics of an adenoma. The tumors were characterized by a marked proliferation of both epithelial and connective tissue cells. The tumor cells produced a large number of irregular-sized and tortuous gland-like structures (Fig. 2). The epithelium varied from simple to stratified columnar. Many of the gland-like structures disclosed large numbers of goblet cells (Fig. 3). Some parts of the adenoma appeared to have been distended with fluid to form cysts. The epithelium of the gland-like structures near the mucosal surface showed extensive desquamation (Fig. 4).

The stroma appeared to be of a loose mixed type in the more normal areas. In other parts of the neoplasm the stroma exhibited numerous lymphocytes, plasma cells and some mononuclear phagocytes. In a few areas concentric rings of collagenous fibers were found around some of the gland-like structures.

In most areas the transitional epithelium of the bladder mucosa had desquamated or was flattened.

Examination of sections stained by the Gram-Weigert method revealed bacteria (*Corynebacterium renale*) among the desquamated cells scattered along the surface of the bladder mucosa. Bacteria were not observed in the neoplastic tissue.

SUMMARY

A microscopic study of the neoplastic tissue from two bovine bladders revealed adenomatous structures with mucin-producing, columnar epithelium. There was no evidence of infiltrative epithelial growth.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 82

FIG. 1. Mucosal surface of bladder showing small nodular adenomas. The white material in the center is a purulent and fibrinous exudate. $\times \frac{1}{2}$.

FIG. 2. Adenoma of bladder showing (A) gland-like structures of adenoma; (B) pseudostratified columnar epithelium; (C) stroma containing large numbers of lymphocytes and plasma cells; (D) goblet cells; (E) separation of the epithelium from the stroma is an artifact. $\times 98$.



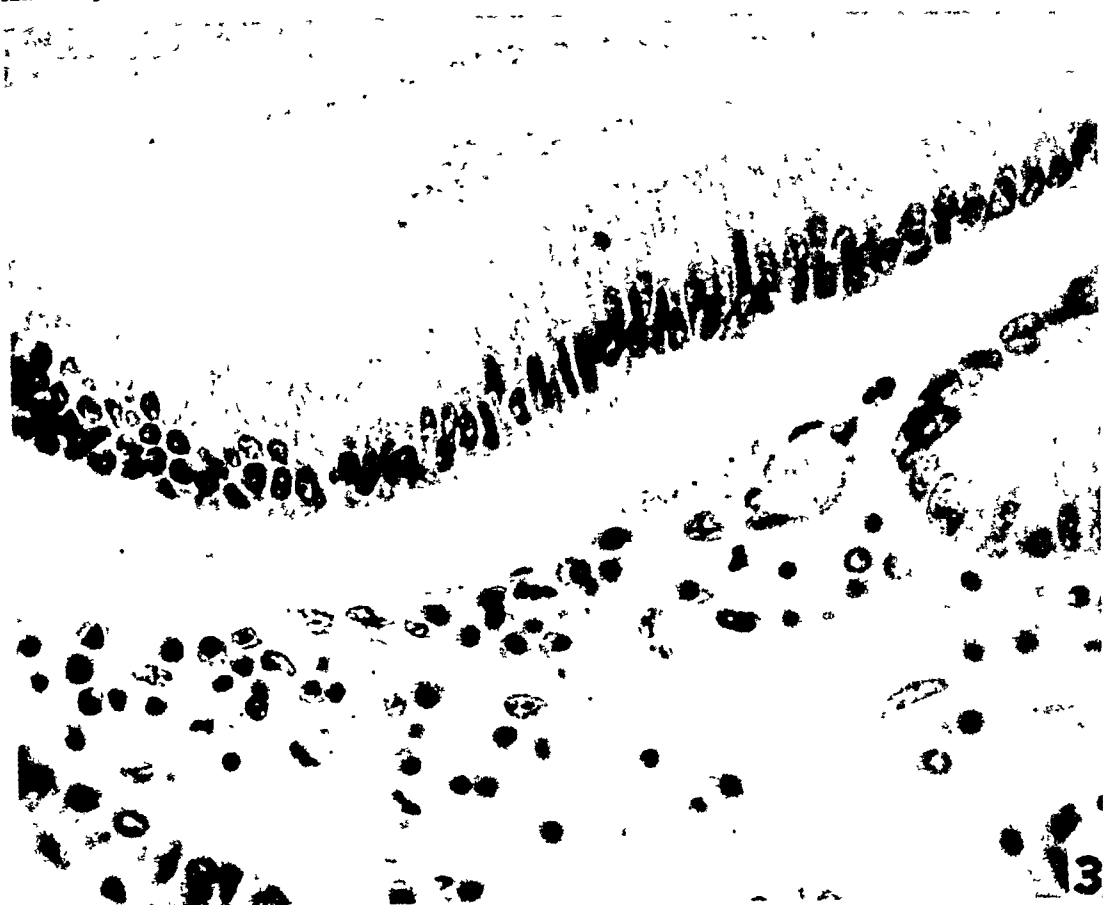
Langham, Thorp and Hallman

Adenoma of the Bovine Bladder

PLATE 83

FIG. 3. Higher magnification of Figure 2. $\times 522$.

FIG. 4. Section showing desquamation of the epithelium and the irregularity in size of the gland-like structures. $\times 98$.



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FATAL HERPES SIMPLEX ENCEPHALITIS IN MAN *

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For many years there has been considerable doubt as to the etiologic relationship between herpes simplex virus and human encephalitis.¹ The confusion has been due mainly to the fact that the virus has been isolated from the brain or spinal fluid of patients with such unrelated diseases as syphilis of the central nervous system about as frequently as it has been recovered from the brain or spinal fluid of patients with encephalitis lethargica.¹⁻⁴ Indeed, herpes virus has been isolated from the spinal fluid of apparently normal persons.¹ Such findings are explained on the basis that a large proportion of the population is believed to carry constantly the herpes virus which may be widely disseminated in the body tissues without causing evident disease.^{1,5,6} For these reasons, herpes may be encountered frequently as a contaminant, and its isolation even from cases of encephalitis would appear to be of doubtful significance in most instances.

Recently, however, two cases have been described which seem to present adequate criteria for establishing the causal relationship between herpes and the meningo-encephalitic manifestations encountered. The first of these was reported by Smith, Lennette and Reames⁷ who isolated herpes virus from the brain of an infant whose encephalitic lesions were unusual in that intranuclear inclusions of the herpetic type were present in many cells. Their presence in the brain of this patient may be considered as evidence of reaction of the host to the virus isolated from his cerebrum. Several other cases have been reported⁸⁻¹⁰ in which such inclusions were described, but their proper evaluation is not possible as the causative agent was never determined.

The second case was that of Armstrong¹¹ who isolated herpes virus from the spinal fluid of an adolescent male with aseptic meningitis. He demonstrated the etiologic importance of this agent by means of serologic studies. Blood taken from the patient during the acute illness

* Received for publication, July 12, 1943.

had little or no capacity to neutralize a known strain of herpes virus, but that taken during convalescence contained neutralizing substances.

The present report describes the clinical and pathological findings in a fatal case of encephalitis with acidophilic intranuclear inclusions in cells of the brain substance. In addition, the results of studies which led to the isolation of an infectious agent from the brain and its identification as a strain of herpes simplex virus are given.

REPORT OF CASE *

History. M. B., a 25-year-old private in the United States Army, was admitted to the Station Hospital at Camp Claiborne, Louisiana, on July 27, 1942. He was unable to give a history. It was learned that he had complained of severe headache for 3 days prior to admission, and had become slow and incoherent of speech. There had been no recent vaccination and no history of herpetic eruption.

Physical Examination. Temperature, 103.8° F.; pulse, 108; respirations, 26; blood pressure, 142/88. The skin was hot and dry. There were no herpetic lesions. The lips and nail beds were slightly cyanotic. The throat was moderately injected. Neurologic examination revealed a conscious, apathetic patient whose answers were unrelated to questions asked. He seemed to know what objects were, but was unable to name them. The left pupil was slightly larger than the right; both reacted well to light and in accommodation. Extra-ocular movements were done well. The optic disks were of good color and showed no papilledema. No impairment of sensation could be detected. There was no paralysis or local motor weakness. A slight increase in tone of the right upper and right lower extremities was present. Deep tendon reflexes were equal and somewhat hypo-active. The plantar responses were normal. The neck was stiff and Kernig's sign was positive bilaterally. The remainder of the physical examination was negative.

Laboratory Findings. Blood. July 27: thick drop preparation was negative for malaria; red blood cells, 4,900,000 per cmm.; white blood cells, 16,200 per cmm.; polymorphonuclear leukocytes, 69 per cent.; lymphocytes, 21 per cent. July 30: white blood cells, 16,000 per cmm.; polymorphonuclear leukocytes, 92 per cent.; lymphocytes, 8 per cent. Culture taken on July 27 showed no growth after 5 days.

Urine. July 27: negative.

Spinal Fluid. July 27: clear; pressure, 180 mm. of water; cells, 175 per cmm., all lymphocytes; organisms, none in smear; culture, no growth; sugar, normal reduction; globulin, 1 plus Pandy reaction; total protein, 44.4 mg. per cent; Wassermann reaction, negative. July 30: fluid flocculent in appearance; pressure, not increased; cell count, 323 per cmm. with 97 per cent lymphocytes; organisms, none in smear; culture, no growth; sugar, normal reduction; globulin, 2 plus Pandy reaction; total protein, 50 mg. per cent.

Roentgenographic Findings. Bedside examinations of the chest on July 28, 29 and 30 showed no evidence of pneumonia.

Clinical Course in Hospital. Following the first lumbar puncture, the patient became slightly more rational than on admission. The next day his temperature reached 105° F. and he continued to be restless, complained of headache, became more drowsy and then completely delirious. During his hospital stay of 5 days, the temperature remained elevated between 103° and 105° F., with a pulse rate of around 110. No further neurologic abnormalities were noted. On July 30, he

* Accession number 85691, Army Institute of Pathology of the Army Medical Museum, Washington, D. C.

became more comatose and developed râles and rhonchi in his lungs. Hiccoughing became quite troublesome. He was given intravenous fluids, and, because of the increasing signs of pneumonia, 5 gm. of sodium sulfathiazole intravenously. However, he became progressively weaker, lapsed into coma, and died on August 1, 5 days after admission. The clinical diagnosis was equine encephalomyelitis.

Autopsy Findings

The autopsy was performed 3 hours post-mortem. Gross pathologic changes were limited to the chest and brain. There was bilateral hydrothorax, with about 500 cc. of clear straw-colored fluid in each pleural cavity. Evidences of bronchopneumonia were present in the dependent portions of the lungs.

The brain was removed without difficulty. The dura was moderately tense. A slight excess of cerebrospinal fluid was noted. The gyri were moderately flattened and the hemispheres were symmetrical. The meninges were smooth and uniform throughout. The vessels over the surface were slightly congested, and there was moderate edema of the parenchyma. The brain weighed 1,350 gm. Along the inferior margin of the left temporal lobe was an area of softening about 4 cm. in diameter. This area was studded with small hemorrhages which on section were seen to extend into the parenchyma.

Microscopic Examination. Significant pathologic lesions observed on microscopic examination were limited to the lungs and the central nervous system. An early confluent bronchopneumonia with an exudate consisting principally of polymorphonuclear leukocytes was found.

Intense vascular congestion was uniformly present in the central nervous system, with many areas of small ecchymoses and petechiae in both the brain substance and subarachnoid area. A moderately severe focal meningitis, with infiltrations of lymphocytes and large mononuclear cells generally occurring about vessels, was found over the cerebral hemispheres and the cerebellum and about the spinal cord.

The most striking lesions in the brain substance were found in the cortex and subcortical white matter, particularly in the vicinity of the area of softening in the left temporal lobe. Perivascular cuffs composed of lymphocytes in the Virchow-Robin spaces were present throughout this region and were occasionally encountered in the midbrain and pons. The endothelial cells lining such vessels were frequently swollen. Proliferated glial cells were numerous in the tissue about the cuffed vessels. Within the area of encephalomalacia in the left temporal region there were numerous small hemorrhages, as well as foci of spongy necrosis and large collections of "Gitterzellen" among which a moderate number of polymorphonuclear leukocytes were visible. Lamination of the cortex was difficult to make out even in areas distant from

the severely affected portion of the temporal lobe. The ischemic necrosis of many scattered nerve cells together with an increase in the number of glial cells was responsible for the disruption of the normal architecture. Necrosis of nerve cells occurred rarely or not at all in the midbrain, pons, cerebellum and cord.

Intranuclear inclusions of the herpetic type were present in profusion in certain portions of the cerebrum. These appeared as bright pink, homogeneous or granular structures occupying most of the space *within the nuclei of cells in sections stained with phloxine and methylene blue or by Giemsa's technic*. Occasionally the characteristic picture of an A type intranuclear inclusion was seen, *i.e.*, a large pink body surrounded by a clear zone in which the blue nucleolus lies close to the dark nuclear membrane which is thickened because of margination of chromatin. Most of the acidophilic inclusions were found in glial cells but a few nerve cells were similarly affected. Inclusions were encountered most frequently in or near those portions of the pyramidal layers where necrosis of cells had occurred. They were seen also in cells deep in the brain tissue in the areas of glial infiltration which surrounded cuffed vessels. Intranuclear inclusion bodies were not observed in sections from the midbrain, cerebellum, pons, or cervical cord.

ISOLATION OF THE VIRUS

Attempts were made to isolate virus from spinal fluid and blood drawn during life, and from spinal fluid and brain material removed at autopsy.

Two days before death, specimens of blood and spinal fluid were shipped frozen to the Army Medical School. Guinea-pigs were inoculated intracerebrally and intraperitoneally with a mixture of the two fluids, and, while transient fever resulted in two animals, no transmissible disease was obtained.

The spinal fluid removed immediately after death proved to be bacteriologically sterile. At the Station Hospital, it was injected intracerebrally into six mice, four of which died after about 3 days. Cultures of the brains were all negative. A suspension was made from two of these, and injected into two more mice. One failed to show signs of illness, but the other succumbed on the third day. Sections of the mouse brains were not interpretable because of post-mortem change. The agent was not maintained because of lack of facilities at Camp Claiborne. However, in the light of later findings, it appears that the virus was present in the spinal fluid obtained at the autopsy.

At the time of autopsy, sections were removed with sterile precautions from the temporal lobe, motor cortex, midbrain, pons, cerebellum and cervical cord. These were placed in sterile buffered glycerin and

sent to the Division of Virus and Rickettsial Diseases at the Army Medical School, where they were received 4 days later. Four separate attempts were made before isolation of the virus was accomplished. Ten per cent suspensions of cerebral tissue were injected intracerebrally and intraperitoneally into guinea-pigs. A febrile response which began in about 5 to 7 days and lasted for several days was the only evidence of disease induced in these animals. Although response of this type was elicited on several occasions, the disease was not transmissible from the original to passage animals.

Approximately 6 weeks after receipt of the glycerinated material, during which interval it had been stored at 5° C., fresh suspensions were prepared and injected intracerebrally into mice and into young adult hamsters.

Three mice received intracerebral inoculations of 0.03 cc. of a 10 per cent suspension of the brain in serum-saline solution. One mouse showed paralysis and convulsions on the eighth day. It was sacrificed and its brain cultured and passed in a like manner to additional mice. These animals died on the fourth day.

The virus* was then maintained by successive mouse passages. The other two original mice failed to develop any evidence of disease. They were later subjected to intracerebral inoculation of fifth-passage mouse brain and found to be immune.

Two young Syrian hamsters were inoculated intracerebrally with 0.05 cc. of the same suspension of original brain material. One became ill on the sixth day. It was sacrificed and its brain passed to two more hamsters, and to mice. The mice died with typical clinical findings for the virus strain, confirming its presence. The other hamster failed to develop evidence of disease. However, its serum was later found to afford a significant degree of protection in neutralization tests against the virus.

Of the second-passage hamsters, one became ill. Though its brain was passed to other hamsters, they failed to develop clinical evidence of disease and this substrain was considered lost.

MANIFESTATIONS OF THE VIRUS IN LABORATORY ANIMALS

Mice. The virus was carried through 33 consecutive passages in mice. In these animals the 50 per cent lethal end-point became stabilized at 10^{-3} to 10^{-4} . Following intracerebral inoculation, the disease usually manifested itself first as a marked hyperactivity to mechanical stimuli. This occurred as early as 24 hours after inoculation, but more commonly after 2 to 3 days. Once this sign appeared, the course was

* The virus isolated from this patient is designated as the "M. B. virus" throughout the text.

generally a rapid one. The animals developed a roughened fur, their gait became spastic, they lost their normal activity, and ate and drank poorly. Death usually occurred following a tetanic convulsive seizure, the front and hind legs extended backwards.

A somewhat different picture was observed in those mice which died following intraperitoneal inoculation with larger amounts of virus. The course was more prolonged, death occurring after a week or more. The animals appeared sluggish, their fur became roughened, but the hyperactivity and convulsive seizures did not usually occur. Death occurred suddenly and rather unexpectedly when compared to the course of mice inoculated intracerebrally. That the brains of such mice contained the virus could readily be demonstrated by intracerebral passage into other mice, which followed the usual clinical pattern.

Hamsters. Three young hamsters (3 to 4 weeks old) were inoculated intracerebrally with 0.05 cc. of a 1:10 dilution of brain from the 17th mouse passage. All were ill on the second day. One was sacrificed for further passage, the second died on the fifth day, while the third recovered. The second-passage hamsters also became ill on the second or third day, as did those of the third passage. Virus from a third-passage hamster brain was titrated intracerebrally in mice and found to kill in dilutions up to and including 1:10,000. Illness in hamsters was manifested principally by hyperactivity, followed by sluggishness, muscular incoordination, tremors, and in some instances paralysis and death.

Intraperitoneal inoculation usually produced no clinical disease in hamsters. However, one of the third-passage hamsters used in the original attempt at isolation of the virus, and which had shown no clinical signs of disease, was inoculated intraperitoneally 24 days later. It received 0.2 cc. of a 10 per cent suspension of brain from the fourth mouse passage. Nine days later, this hamster developed paralysis of the hind legs. It was sacrificed and brain material in 1:10 and 1:100 dilutions was injected intracerebrally in mice. These died in the expected manner, indicating the presence of the virus.

Guinea-pigs. Two guinea-pigs received 0.1 cc. intracerebrally of a 1:10 suspension of mouse brain from the 10th serial passage. Both animals had fever from the fourth day. One showed weight loss and kyphosis. It underwent generalized clonic convulsions on the seventh day. The other animal was sacrificed on the sixth day. Its brain was passed intracerebrally to additional guinea-pigs and mice. These guinea-pigs had a mild elevation of temperature from the fourth to sixth days, then recovered. The mice, however, died from 3 to 5 days following inoculation.

Intracutaneous and foot-pad inoculations were also done in guinea-pigs. Red papular lesions appeared at the sites of intracutaneous inoculation on the second day, subsiding in 2 to 3 days. One such lesion developed a vesicle before resolving. The inoculated foot pads became inflamed and swollen on the second day, the reaction gradually subsiding in the course of a few days. Lesions of the skin and foot pads were surgically removed, ground, suspended in serum-saline solution and similar inoculations were made in other guinea-pigs with comparable results. The presence of virus in these lesions was verified by mouse inoculation. There were no deaths among guinea-pigs inoculated through peripheral routes.

Rabbits. Three rabbits were inoculated with a suspension of potent mouse-brain material on the scratched corneal surface. One showed clouding of the cornea on the second day. This progressed to a marked keratitis and conjunctivitis. The animal also developed signs of encephalitis and was sacrificed on the fifth day. Brain was titrated in mice, only a small amount of virus being present. The second rabbit developed marked conjunctivitis, keratitis and iritis. The process gradually resolved, and the animal recovered without developing encephalitis. No corneal or encephalitic disease was observed in the third rabbit.

Two rabbits received intracutaneous and subcutaneous inoculations of infectious mouse brain without the production of significant lesions. Negative results were obtained also with intracerebral inoculations of two rabbits.

Rhesus Monkey. An old monkey, which had been used for other studies, was inoculated with a 10 per cent suspension of brain material of known infectivity from the 20th mouse passage. It received 0.4 cc. intracerebrally, 0.4 cc. subcutaneously, as well as scratch inoculations of the skin and cornea. No fever or lesions resulted.

Chorioallantoic Membrane of Developing Chick Embryo. The virus was carried through five successive transfers on the chorioallantois of developing chick embryos. Opaque central plaque lesions were seen on the second and third day following inoculation. These lesions were surrounded by smaller pock-like foci. Grossly and microscopically the lesions resembled, in general, those described for herpes simplex virus.^{12, 13}

PATHOLOGY OF BRAINS OF EXPERIMENTAL ANIMALS

Histopathologic studies were employed as an ancillary aid in the identification of the M. B. agent. Selected tissues from infected rabbits, mice, guinea-pigs and hamsters, and the chorioallantoic mem-

branes of embryonated eggs were fixed in acetic Zenker's solution, and paraffin sections were prepared and stained by a modification of the Romanowsky technic. The lesions were similar to those described by others in studies of experimental herpes (van Rooyen and Rhodes,¹ Smith, Lennette and Reames⁷). Particular attention was paid to the changes in the brains of mice since these animals were used most extensively, and of hamsters for their response to herpes virus has not been previously described.

It seems worth while to emphasize the characteristic microscopic findings in brains of mice that died 2 to 3 days after intracerebral inoculation with a well adapted neurotropic strain of herpes virus. Infiltrative phenomena, *i.e.*, perivascular collections of lymphocytes in the brain substance and in the meninges, had not yet appeared. Moreover, examination under low power showed little except focal areas in which nerve cells stained poorly. Closer study of such areas revealed the presence of necrobiotic changes which ultimately reach necrosis. In the less severely affected cells the classical intranuclear inclusions of herpes could be found. Mice that died following a more prolonged incubation period developed the meningo-encephalitis usually described; however, intranuclear inclusions were difficult to find in such brains. When present, they were usually encountered about the perimeter of fresh areas of necrosis.

The primary cellular changes induced by various viral infections range from those almost entirely degenerative to those almost entirely proliferative; while inflammatory reactions, as evidenced by infiltrative phenomena, are secondary lesions.¹⁴ The early lesion of herpes simplex in the mouse brain is essentially degenerative in character. Histo-pathologic changes encountered in the brains of hamsters, rabbits and guinea-pigs infected with the mouse-adapted strain of M. B. virus were similar to those observed in mice; intranuclear inclusions of the herpetic type were found in each species. In addition, a few intranuclear bodies were observed in the proliferating ectodermal cells in the pock-like lesions on the chorioallantoic membranes of eggs inoculated with the M. B. virus.

IDENTIFICATION OF THE M. B. VIRUS

The cardinal feature of the microscopic pathology in both the human and the animal brain was the presence of acidophilic intranuclear inclusion bodies in the nerve cells. Such inclusions are especially associated with infection with herpes simplex, B virus and pseudorabies.¹ Separation of M. B. virus from B virus and pseudorabies was suggested by the differences in host range, routes of infectivity, and clinical

course in experimental animals. For example, B virus produces encephalitis irregularly in mice inoculated intracerebrally, and Sabin¹⁵ was unsuccessful in several attempts at mouse passage with brains of mice sacrificed at the height of the disease. In addition his results from inoculations of rabbits with B virus were more pronounced than those we obtained with the M. B. strain. Pseudorabies was considered improbable since none of the rabbits inoculated with the M. B. virus exhibited the characteristic "mad-itch" syndrome ascribed to it.¹ It was apparent, therefore, that we were most likely dealing with a strain of herpes simplex virus. The following studies were undertaken to explore this possibility.

Experiments Designed to Establish the Identity of the M. B. Virus. The methods used to identify the M. B. strain of virus included the observation of the R. T. strain* of herpes simplex in parallel animal experiments, as well as cross-immunity and cross-neutralization tests.

The routes of infectivity, period of incubation, clinical course, type of death and pathologic findings for both strains of virus were essentially identical in mice, hamsters, guinea-pigs, rabbits, and the chorio-allantoic membranes of developing chick embryos.

Cross-Immunity Tests in Mice. Mice were immunized with some difficulty to our strain (M. B.) of virus and to the known strain (R. T.) of herpes simplex. Immunization was accomplished by repeated injections of the virus in graduated doses. Two or three injections were made subcutaneously and then intraperitoneally, at intervals of a few days to a week apart. Finally, an intracerebral inoculation with the homologous virus was made to test for immunity.

In the course of these experiments, 11 mice were immunized with M. B. virus (Table I). Ten of these survived intracerebral inoculation with the R. T. virus, 1 animal dying 14 days after inoculation, probably from intercurrent infection. All normal control mice died after undergoing the characteristic course.

In the reverse cross, five mice, which had been immunized with R. T. virus, were tested. All survived intracerebral inoculation of a 1:10 dilution of the M. B. virus. The control animals all died.

Cross-Neutralization Tests in Mice. The preparation of potent neutralizing sera for herpes simplex virus is difficult.^{7, 11} In general, our efforts with the M. B. virus and the R. T. strain proved to be no exception. Guinea-pigs, rabbits, hamsters and one monkey (receiving M. B. virus) were repeatedly inoculated subcutaneously and intraperitoneally with suspensions of infected mouse brain. Three to five

* The R. T. strain of herpes simplex virus was kindly furnished us by Dr. Margaret M. Smith.

injections were given each animal at intervals of a few days to 2 weeks, with a final intracerebral inoculation to check immunity to the virus strain used. After a period of 2 weeks or more from the last injection, the animals were bled.

Neutralization tests were carried out in the following manner: suspensions of fresh* infected mouse brain in sterile serum-saline solution were made up in serial ten-fold dilutions. Equal amounts of the virus dilution and of serum were thoroughly mixed, incubated in the water-bath at 37.5° C. for 1 hour, then inoculated intracerebrally into mice.

TABLE I
Cross-Immunity Tests in Mice: M. B. Virus and Known Herpes Simplex Virus (R. T. Strain)

Experiment	Immunized with	Tested with*	Deaths among tested mice	
			Immunized	Normal
I	A	M. B. virus	0, 0, 0, 14†	7, 7, 7, 10
	B	M. B. virus	0, 0	3, 3, 3, 3, 3, 4
	C	M. B. virus	0, 0	2, 3, 3, 3, 3, 3
	D	M. B. virus	0	4, 4, 4, 4, 4, 4
	E	M. B. virus	0, 0	4, 5, 5, 6, 7, 7
II	A	R. T. virus	0	2, 2, 3, 3, 3, 3
	B	R. T. virus	0, 0, 0, 0	3, 3, 3, 4, 4

* Test dose consisted of an intracerebral inoculation (0.03 cc.) of a 10^{-1} dilution of fresh infected mouse brain. Such a suspension of virus contained 10^3 to 10^4 MLD.

† This mouse probably died of intercurrent infection; the numeral indicates day of death of mouse following test inoculation; 0 indicates mouse survived.

Daily observations of the mice were continued for 18 days following inoculation.

Though not so striking as desirable, the results supported the cross-immunity findings, which indicated a close similarity of the two strains of virus. In general, the immune sera protected against three to five times as much virus of both strains as did the control sera. In Table II are given the results obtained in two experiments with guinea-pig sera. Comparable results were obtained in tests with monkey, hamster and rabbit sera. In some instances, sera gave better protection against the homologous virus strain than against the heterologous strain, while in others the reverse was noted.

SUMMARY

A virus was isolated from the brain of a fatal case of acute encephalitis. Acidophilic intranuclear inclusion bodies were present in the

*Fresh mouse brain was used since it was found that the potency of the two virus strains rapidly declined when stored at -70° C. Such fresh material repeatedly yielded a titer of 10^{-3} or better when tested intracerebrally in mice.

TABLE II
Cross-Neutralization Tests: *M. B. Virus and Known Herpes Simplex (R. T. Strain)*
with Guinea-Pig Sera

		Experiment I				Experiment II		
Virus strain	Virus dilution	Normal serum	M. B. immune* pool 811-812	R. T. immune pool 806-808	Normal serum	M. B. immune 455	R. T. immune 341	
M. B.	10 ⁻¹	4, 4, 5, 6, 7, 7†	0, 0, 0, 0	4, 4, 4, 5	
M. B.	10 ⁻²	6, 6, 6, 7	5, 5, 6, 7	6, 6, 6, 9, 9, 18	10, 0, 0, 0	8, 10, 10, 11	
M. B.	10 ⁻³	4, 4, 5, 6	7, 7, 8, 0	6, 8, 11, 0	7, 14, 15, 0, 0, 0	0, 0, 0, 0	7, 0, 0, 0	
M. B.	10 ⁻⁴	5, 7, 8, 10	0, 0, 0, 0	15, 0, 0, 0	10, 0, 0, 0, 0	
M. B.	10 ⁻⁵	8, 8, 0, 0	
M. B.	10 ⁻⁶	13, 0, 0, 0	
Virus titer		10 ^{-5.2}	10 ^{-3.3}	10 ^{-3.5}	10 ^{-3.2}	< 10 ^{-1.0}	10 ^{-2.7}	
R. T.	10 ⁻¹	3, 3, 4, 4, 4, 4	6, 7, 9, 9	4, 5, 5, 5	
R. T.	10 ⁻²	0, 0, 0, 0	7, 7, 8, 11	4, 5, 5, 5, 7, 7	11, 13, 0, 0	5, 6, 6, 7	
R. T.	10 ⁻³	6, 11, 0, 0	10, 0, 0, 0	0, 0, 0, 0	5, 5, 6, 7, 7, 8	9, 0, 0, 0	10, 11, 12, 12	
R. T.	10 ⁻⁴	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0	8, 10, 10, 13, 0, 0	
R. T.	10 ⁻⁵	0, 0, 0, 0	
R. T.	10 ⁻⁶	0, 0, 0, 0	
Virus titer		10 ^{-3.0}	< 10 ^{-2.0}	10 ^{-2.5}	10 ^{-4.3}	10 ^{-2.2}	At least 10 ^{-3.5}	

* Guinea-pigs received repeated subcutaneous and intraperitoneal injections of the virus strain and an intracerebral challenge with the same virus before being considered immune.

† Numeral indicates day of death of mouse following intracerebral inoculation of serum-virus mixture; 0 indicates mouse survived at least 18 days.

affected brain cells of the patient, and were also produced in experimental animals. The presence of these bodies suggested that the virus agent belonged to the group which includes herpes simplex, B virus and pseudorabies. Elimination of B virus and pseudorabies was based on the type of response elicited in laboratory animals. Identification of the M. B. virus as herpes simplex was made through cross-immunity tests and cross-neutralization tests with a known strain (R. T.) of herpes virus.

This is the second case of fatal herpes simplex encephalitis associated with acidophilic intranuclear inclusions from which the virus has been isolated and its etiologic relationship established.

We wish to thank Capt. H. Hamilton, Sn. C., who carried out the chorioallantoic studies, and Lt. K. Wertman, Sn. C., who assisted with the earlier animal work. Many members of the Virus Division of the Army Medical School contributed valuable assistance in the course of these studies.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 84

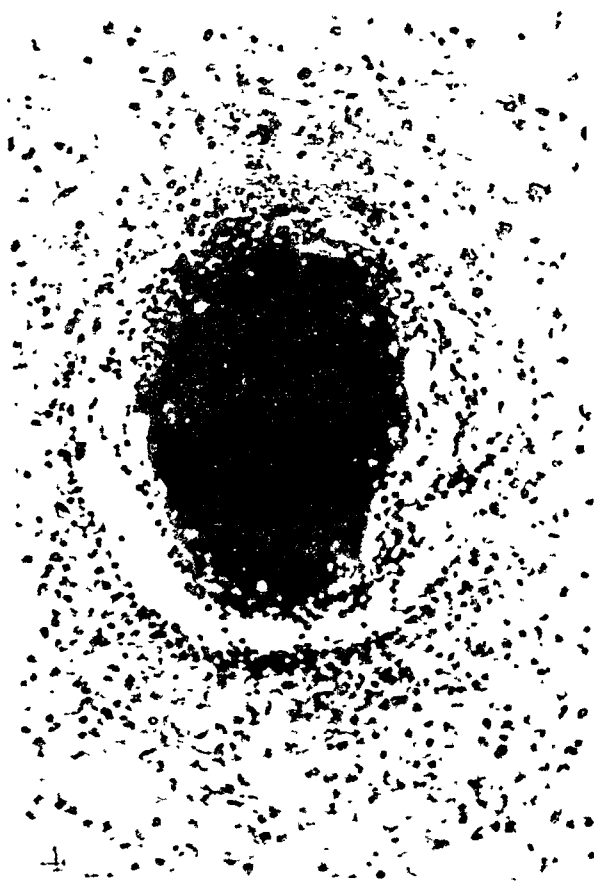
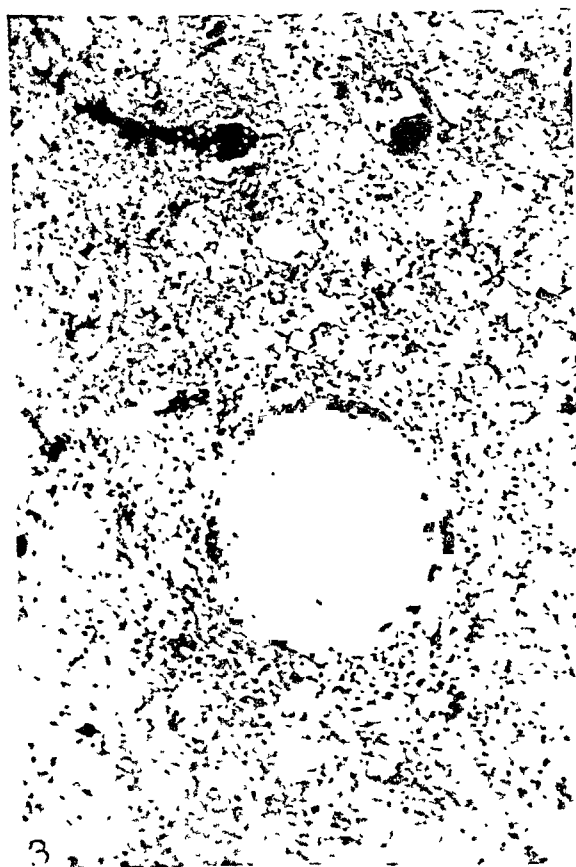
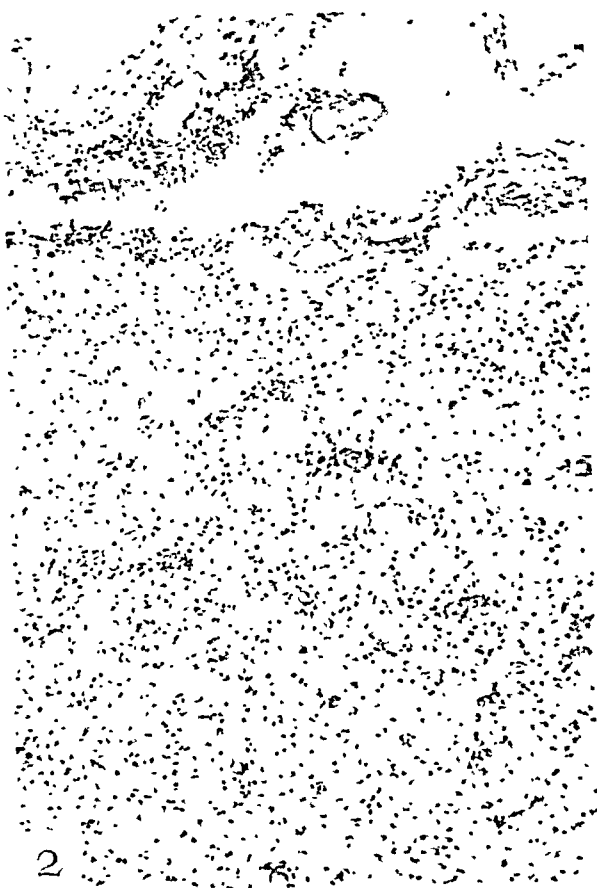
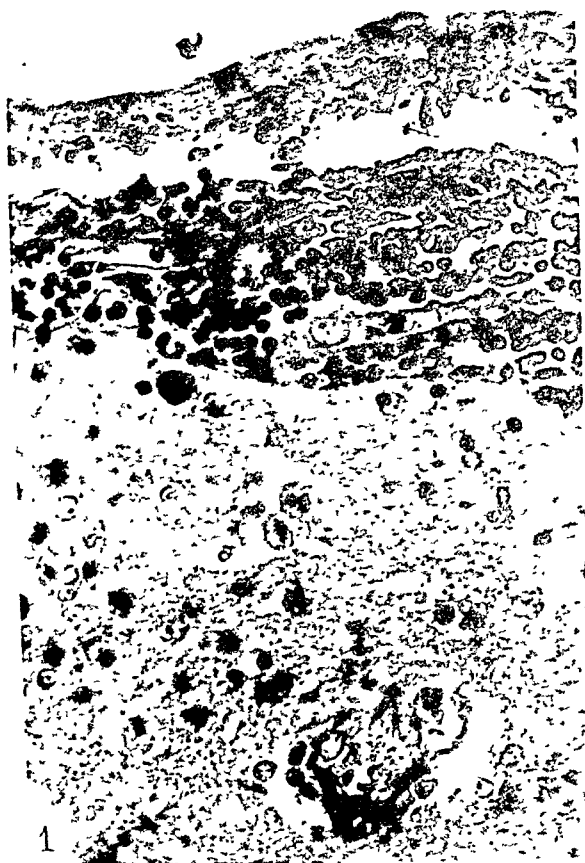
Pathologic changes in the brain of a patient with herpes encephalitis. The sections were stained with hematoxylin and eosin.

FIG. 1. The leptomeninges contain lymphocytes, and the underlying cortex is infiltrated with microglia and astrocytes. $\times 370$.

FIG. 2. Leptomeninges and cortex. The ganglion cells are in a state of degeneration. The cortex contains numerous microglia and a few astrocytes. $\times 90$.

FIG. 3. Subcortical white matter. The tissue is in part necrotic. Microglial cells are accumulated in the extra-adventitial tissue. $\times 115$.

FIG. 4. Subcortical white matter. The Virchow-Robin space surrounding the vessel contains numerous lymphocytes. The extra-adventitial tissue is crowded with Gitterzellen. $\times 115$.



Zarafonitis, Smadel, Adams, and Haymaker

Herpes Simplex Encephalitis in Man

PLATE 85

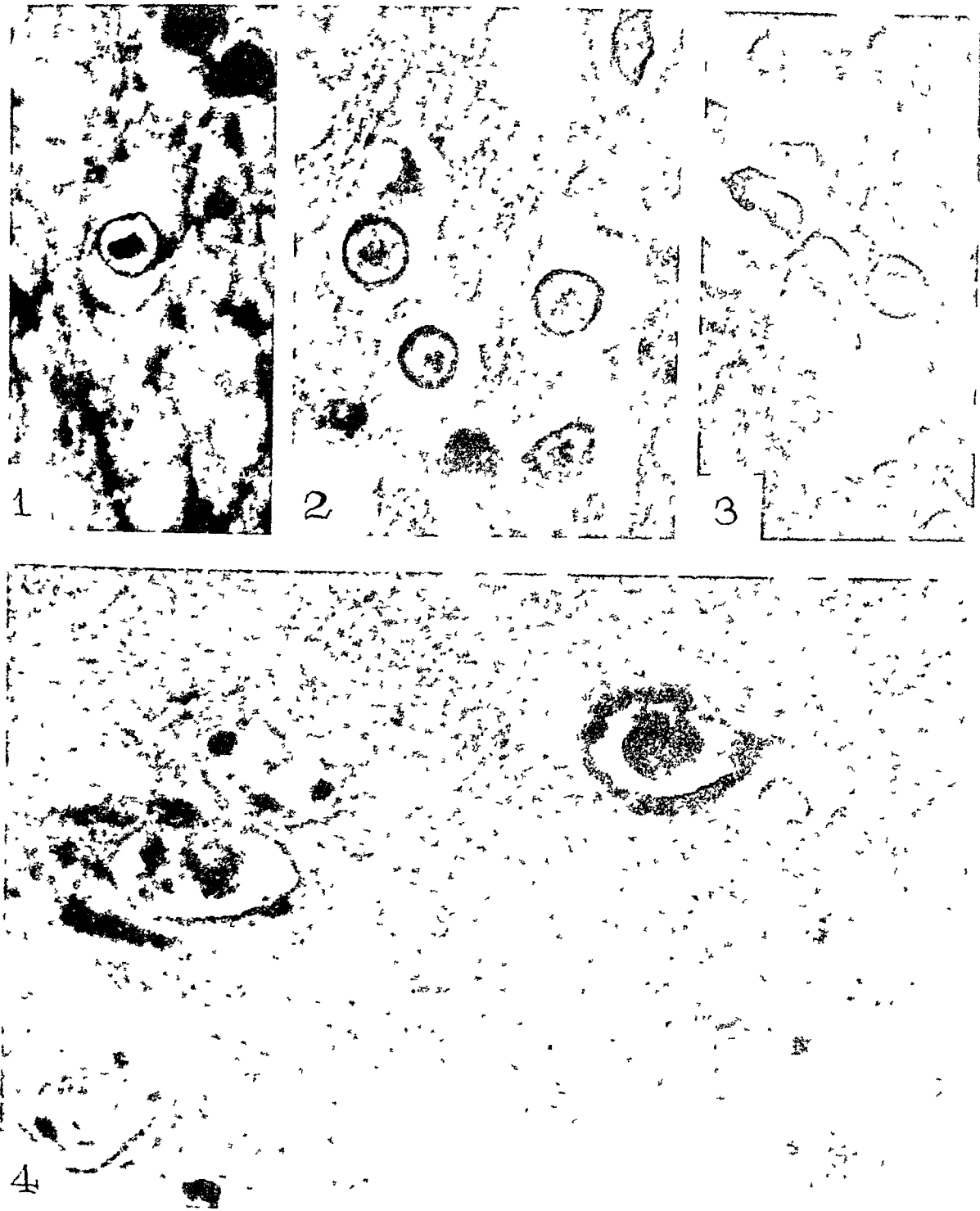
Intranuclear herpetic inclusions in human and murine brains. The sections are stained with phloxine and methylene blue.

FIG. 1. Intranuclear inclusions in human brain. $\times 1075$.

FIG. 2. Intranuclear inclusions in human brain. $\times 1075$.

FIG. 3. Intranuclear inclusions in human brain. There is margination of the nuclear chromatin. $\times 1075$.

FIG. 4. Intranuclear inclusions in brain of mouse. One of the inclusion bodies has a homogenous appearance; the other is granular. $\times 2150$.



Zarafonetis, Smadel, Adams, and Haymaker

Herpes Simplex Encephalitis in Man

INFECTION OF HUMAN SKIN, GRAFTED ON THE CHORIOALLANTOIS OF CHICK EMBRYOS, WITH THE VIRUS OF HERPES ZOSTER *

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Although herpes zoster has not been undoubtedly transmitted to experimental animals there is good evidence that its causative agent has been successfully inoculated into human beings and that it is a virus. The first to accomplish human inoculation was Kundratitz¹ in 1925. In his first experiments three children were inoculated after scarification on the upper arm, with clear contents of zoster vesicles. In two of these, after 11 days, there appeared in the area of inoculation several clear vesicles with a slight reddening of the periphery. The appearance corresponded quite completely with inoculatory vesicles of varicella first induced locally in man by Kling² in 1913. The vesicles healed during 2 or 3 days and became dry.

Following these first positive results Kundratitz inoculated material from nine typical cases of thoracic zoster into human skin. Material from four of these resulted in typical vesiculation locally in the skin of several children. The reaction appeared 9 to 12 days after inoculation.¹

In 1921, Lipschütz³ described acidophilic intranuclear inclusions in the cutaneous lesions of zoster which he considered to be specific. His observations have been repeatedly confirmed and now the presence of acidophilic intranuclear inclusions is regarded as the most specific characteristic of the zoster lesion, although the inclusions are indistinguishable from those first described by Tyzzer⁴ in cutaneous lesions of varicella. Their presence is taken to signify the effect of a virus. Kundratitz removed some of his experimental lesions and submitted them for histological study to Lipschütz who demonstrated in them the characteristic inclusions. The successful inoculations were in children under 5 years of age, some of them nurslings; those in older children were negative.

The etiological agent of herpes zoster has never been successfully inoculated into any animal in series other than man, although Lipschütz³ and Marinesco and Draganesco⁵ reported the presence of acidophilic intranuclear inclusions in the corneal epithelium of rabbits after inoculation with vesicular contents. Others, including Cole and Kuttner,⁶ who reviewed the subject, failed to confirm these results.

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Further light on the nature of zoster virus and its relation to other viruses, especially that of chicken-pox which some investigators believe to be identical, awaits the discovery of a susceptible experimental animal other than man, or the development of a technic by means of which these important problems can be studied.

In attempts to devise a method of this sort, Goodpasture, Douglas and Anderson,⁷ in 1938, succeeded in grafting human skin onto the chorioallantois of chick embryos so that it would survive for several days. Such human skin grafts were successfully inoculated with the viruses of herpes simplex, variola and vaccinia, but all of our attempts to infect the grafts with the virus of chicken-pox failed and in only one set of experiments, out of several, in which human skin grafts were inoculated with the clear fluid from zoster vesicles, did we succeed in inducing specific lesions of this disease. Inoculations of grafts of human fetal membranes (amnion, chorion) with material from vesicles of varicella and zoster were all unsuccessful.⁸

Although we succeeded only once after several attempts in infecting with zoster virus human skin grafted on the chick's chorioallantois, we decided to describe our positive results in the hope that others might have more favorable opportunity to use the method with success. The problem of obtaining suitable skin for grafting and at the same time to be in possession of uncontaminated fluid from zoster vesicles we found to be a difficult one, especially because our facilities permitted us to obtain only minimal quantities of fluid from occasional cases of zoster.

HUMAN SKIN GRAFTS

The technic for grafting human skin onto the chorioallantois of chick embryos we have previously published⁷ in detail and it need not be repeated here. We will therefore describe only the materials and conditions of our successful experiments with zoster, the circumstances of which possess some points of interest.

Source of Human Skin for Grafts. The patient was a white woman, 57 years of age, upon whom a radical mastectomy was performed for scirrhus carcinoma of the right breast. The defect was closed with a single Thiersch graft taken from the right thigh. Pieces of this skin were used to graft on the chorioallantois of 12 9-day-old chick embryos.

It is of interest that the donor gave a history of an attack of shingles in the right thoracic region 8 months previous to her operation.

Source of Herpes Zoster Virus. Clear, vesicular fluid was removed from a band of eruption extending across the right side of the back and into the axilla of a child, 2½ years old. This child had experienced a typical attack of chicken-pox 1 year before admission for zoster.

The clinical description of the zoster eruption was as follows: Starting at the midline in the back at about the second thoracic vertebra there was a band of splotchy erythema about 2 cm. in width extending anteriorly to the midsternal line. There was one small erythematous patch, 1.5 cm. in diameter, high in the axilla upon which were multiple small vesicles not larger than 1 mm. in diameter. Several more patches of blisters were situated anteriorly in which the vesicles were much larger. It was from the latter, especially, that material was obtained for inoculation of the grafts. There was no pustulation.

INOCULATION OF THE GRAFTS

The skin was prepared by the surgical routine for grafting consisting of scrubbing with soap and water and the application of tincture of iodine which was followed by alcohol. After removal, pieces of skin were delivered to us in moist sterile gauze. These pieces were spread out on sterile cork blocks with the epidermis upward. They were cut into 1 cm. squares. Upon the epidermis of each was placed a drop of undiluted vesicular fluid from the syringe in which it was aspirated. With the syringe needle (size 27) multiple punctures were made through the fluid into the surface of the skin. An attempt was made to keep all of the fluid confined to the central portion of the graft. After puncturing, the graft was left for 1 hour on the cork, moistened along the edges with sterile saline solution and lightly covered with moist gauze. This was done in order to allow the vesicular fluid to be absorbed by the skin while the underlying corium was kept in a moist state.

Each graft was then placed upon the chorioallantois of a 9-day-old chick embryo in the manner we have previously described. The grafts adhered successfully and the eggs were incubated for 4, 6, 7 and 8 days, at which intervals living eggs were opened and the grafts with the adherent chorioallantois were removed and fixed in Zenker's solution for histological study. Suggestive but indefinite pin-point lesions were seen grossly on some of the grafts.

After paraffin embedding, sections were stained with hematoxylin and eosin.

DESCRIPTION OF THE LESIONS

Five grafts removed from this series of embryos showed microscopical lesions which were interpreted as evidence of infection with the virus of herpes zoster. One of these was fixed 4 days after inoculation and grafting, 1 on the sixth day, 2 on the seventh day and 1 on the eighth day. Grafts made on the fourth and sixth day showed small foci in an early stage of development; the 8-day graft contained larger

and pustular foci, as many as three being present in a single section. That the foci of infection corresponded with points of puncture at the time of inoculation was indicated in some by the presence of a foreign body reaction beneath the center of the lesion in the chorion or underlying chorioallantois, where evidently a minute fragment of keratin was forced through.

The earliest lesions consisted of small groups of hyperplastic epithelial cells situated in or near the basal layer and free from inflammation. Both cytoplasm and nuclei were swollen and each of the latter contained within its clear nucleoplasm a large, compact acidophilic body. The nuclear chromatin and often the nucleolus were situated peripherally next to the thin nuclear membrane. In older lesions the number of cells involved was much greater, the individual cells were enormously swollen, the enlargement involving both cytoplasm and nucleus. In the center of such a focus the epithelial cells were separated one from another by inflammatory fluid and cellular exudate consisting largely of chick leukocytes. Cellular exudate was present in the corium and underlying chorioallantois, especially abundant about blood vessels. Lying here and there in the purulent exudate of the infected epithelial layer were occasional multinucleated epithelial giant cells, each nucleus or nuclear lobule of which contained an acidophilic inclusion.

The lateral margins of these larger foci showed an extension of the infection to adjacent groups of epithelial cells. These cells were swollen, pushed apart by fluid and contained intranuclear acidophilic inclusions, but there was no cellular exudate.

Few of the involved epithelial cells, even in the most advanced lesions, were evidently necrotic; only rare ones stained so deeply with eosin as to indicate death. In none of the lesions had sufficient fluid accumulated to cause gross vesiculation.

In none of the specimens was there evidence of infection of chick cells as would be indicated by the presence of intranuclear inclusions. In spite of numerous attempts we have never been able to induce in any chick tissue lesions indicative of infection with material from herpes zoster. This is in contrast with the susceptibility of chick embryo tissues, including the chorioallantois, to the virus of herpes simplex.

DISCUSSION

There is acceptable evidence that the characteristic lesion of both varicella and herpes zoster can be induced locally by direct inoculation of the respective vesicular fluid in scarified human skin.^{1, 2} Our failures thus far with chickenpox, and similar numerous failures with zoster,

in attempts to infect grafts of human skin and fetal membranes, amnion and chorion, leave us without an adequate explanation. Although it might be assumed that the original grafts were immune to these viruses, we have demonstrated in other experiments with skin of chickens immune to fowl-pox and human skin immune to vaccinia that, when grafted onto the chorioallantois, the acquired immunity is lost and susceptibility returns.⁹ In the successful experiments herein reported there was good reason to believe that the donor was immune to zoster inasmuch as she had experienced an attack of shingles only 1 year previously.

Reports of successful human transmission of cutaneous infections with the viruses of chicken-pox and of herpes zoster have indicated the first appearance of lesions in 8 to 11 days, whereas following inoculation with herpes simplex lesions appear in 2 to 4 days. In our successful experiments with zoster the first lesions without inflammation appeared in grafts of 4 days' duration, whereas with herpes simplex full-blown lesions occur in 2 to 3 days.

Most successful transmission experiments with zoster fluid have been in infants or children under 5 years of age, possibly because of lack of acquired immunity. In our experiment skin grafts were from an adult 57 years of age, and presumably these grafts lost their acquired immunity as a result of transplantation to the chick embryo. As is the case in infection of grafts of human amniotic epithelium with the virus of mare abortion, the successful inoculations of human skin with zoster fluid demonstrate that a natively susceptible tissue grafted on a naturally insusceptible host (chick embryo) does not thereby lose its susceptibility.⁸

In view of our negative results in several similar attempts to infect human grafts with zoster fluid the thought has occurred to us that the skin of some persons might be especially susceptible to this virus as indicated possibly by a previous attack of shingles in our donor. On the other hand, our successful experiment occurred in the only series in which both fresh zoster fluid and fresh skin were obtained and used on the same day; and this fact might have contributed in some way to the positive outcome.

In spite of several attempts we have not yet succeeded in infecting human skin or fetal membrane grafts with the virus of chicken-pox. If this technic were developed so that both varicella and herpes zoster could be uniformly induced in grafts of human tissue, there would be the possibility of using it to determine the relationship of these viruses to each other, and to discover some of their properties in the absence of a susceptible experimental host other than man.

Our experiments indicate that the epithelial cells of human skin may be immediately susceptible to the zoster virus and that an initial infection of nervous tissue is not essential to the development of a cutaneous eruption.

Notwithstanding the development of a local pustular lesion in the grafted skin, associated with swelling and disruption of cellular contacts and the appearance of multinucleated epithelial giant cells, the final criterion of infection with the zoster virus is the presence of intranuclear acidophilic inclusions indistinguishable from those in the lesions of chicken-pox, as first described by Tyzzer,⁴ and those of zoster, as noted first by Lipschütz.³

Because of the fact that clinically and histologically the eruptive cutaneous lesions of chicken-pox and zoster may be indistinguishable, and the further fact that clinically chicken-pox may be associated with a zosteriform lesion and that zoster may be associated with a generalized nonneural cutaneous eruption, it is of great importance to use typical clinical cases of these diseases in experimental attempts to demonstrate and transmit a specific virus.

The lesions induced in human skin grafts inoculated with zoster fluid do not closely resemble those of herpes simplex in similar tissue. In the latter the inclusions become much larger, often filling the nucleus; and they acquire a basophilic staining reaction.⁸ Simplex virus rapidly kills the cell, causing ulceration and an excessive purulent exudation.

Experimental zoster lesions in grafted human skin serve to throw some light on the pathogenesis of the zoster eruption, a subject which is still a matter of controversy. Only recently a review by Baird¹⁰ so overemphasizes the participation of a neurovascular mechanism as to imply a denial of the local presence of a virus in the skin. No mention is made in that paper of cellular inclusions in the vesicles of zoster.

It is clear from our experiments that lesions composed of epithelial cells containing the zoster inclusions and later infiltrated with chick leukocytes can follow inoculation of human skin removed from its normal nervous and vascular connections. The failure of these lesions to develop completely as vesicles indicates the importance of neurovascular connections for the formation of the abundant serous exudate in the human eruption, but these relations to nerves and vessels do not determine the specific character of the lesions.

CONCLUSIONS

1. Grafts of human skin on the chorioallantois of chick embryos were successfully infected with the virus of herpes zoster.

2. The experimental lesions did not vesiculate grossly but became pustular, and otherwise resembled those in the natural disease, including the presence of intranuclear acidophilic inclusions, first described by Lipschütz,³ in the affected epithelial cells.

3. The tissues of the chick embryo appear to be nonsusceptible to this virus.

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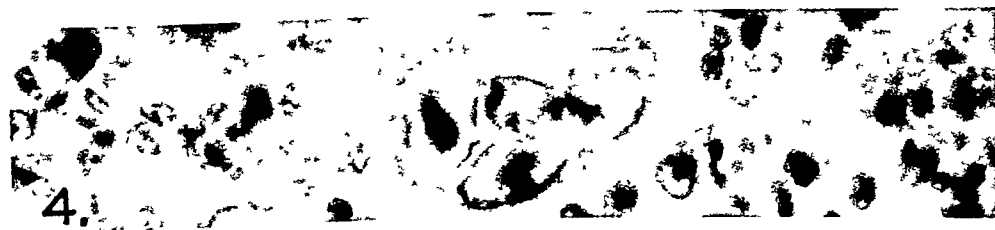
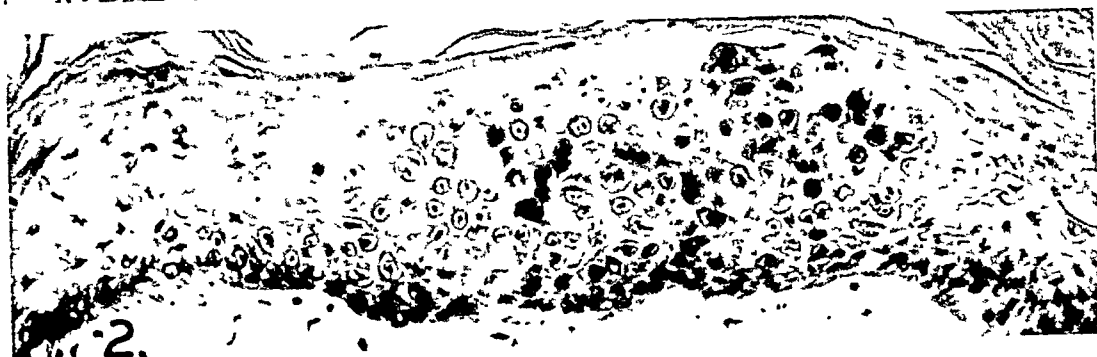
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[Illustrations follow]

DESCRIPTION OF PLATE

PLATE 86

- FIG. 1. Pustulating zoster lesion in human skin graft. (8 days.)
- FIG. 2. Early (6 days) nonexudative zoster lesion in grafted human skin. Swollen, detached epithelial cells are shown, containing intranuclear inclusions. $\times 225$.
- FIG. 3. Intranuclear inclusions from the lesion shown in Figure 1. $\times 1200$.
- FIG. 4. Epithelial giant cell with intranuclear inclusions from Figure 1. $\times 1200$.



EXPERIMENTAL INFECTION OF THE CHICK EMBRYO WITH VIRULENT AND AVIRULENT PASTEURELLA PESTIS *

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The recent use of avirulent live strains of plague bacilli as vaccines for human immunization in several parts of the world has stimulated renewed interest in the biologic nature of this "avirulence." In earlier communications^{1, 2} it was pointed out that virulence in plague apparently is independent of the possession of an envelope and that the most striking *characteristic of avirulent organisms is their inability to proliferate freely even in susceptible experimental animals*, although a complete permeation of the tissues of such animals can readily be observed. One of the principal difficulties of clear-cut differentiation between slightly virulent and completely avirulent organisms is the sliding scale of virulence that is observed when virulence tests of plague bacilli are performed in the common laboratory animals.

Buddingh and Womack³ have studied the infection of the chick embryo with large doses of virulent *Pasteurella pestis*. Their findings indicate a high and uniform susceptibility of this host to plague infection. In order to investigate further the characteristics of the host-parasite relationship that may play a rôle in the determination of virulence or avirulence of plague bacilli, the experimental infection of chick embryos with known numbers of virulent and avirulent *P. pestis* was undertaken. This work involved the determination of relative susceptibility to, and reactions induced by, inoculation of various doses of plague bacilli into chick embryos. The observations on survival time, bacterial multiplication and persistence were supplemented by a histologic study of the changes resulting from infection with plague bacilli in the chorioallantoic membrane and the organs of the chick.

MATERIALS AND METHODS

The strains of *P. pestis* used in this study (virulent strain 106 and avirulent strain A1122) have been described previously.² Chick embryos of 11 to 14 days' incubation were inoculated with 0.1 ml. of broth culture dilutions in saline solution, containing a known number of live bacilli.² The technic followed was that of Goodpasture and Buddingh⁴ for inoculation of the chorioallantois, while the methods of Polk, Buddingh and Goodpasture⁵ and of Cox,⁶ respectively, were used for

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injection of amniotic space or yolk sac. The inoculated eggs, together with suitable controls, were incubated at 37.5° C. and either observed for survival of the infection and hatching or killed at 24-hour intervals, the membrane and organs cultured¹ and pieces fixed in Zenker's fluid (with 4 per cent formaldehyde) for histologic sections. The sections were stained with hematoxylin and eosin as well as by Giemsa's method which permits the easy detection of plague bacilli in tissues.

Chicks that survived the infection with small numbers of avirulent *P. pestis* were killed at intervals after hatching and their organs cultured in order to determine the survival of avirulent bacilli. The culture methods used were the same as previously described.¹ In several experiments the practicability of serum protection tests with antiplague rabbit sera in chick embryos was tested. The influence of immune serum on the development and extent of lesions caused by virulent and avirulent plague bacilli was also studied. The antiplague immune serum which was produced by the injection of live avirulent organisms² had an anti-envelope agglutination titer of 1:320, and a protection titer of 25 provisional standard units.⁷ One-tenth ml. of this serum diluted 1:2 was dropped onto the chorioallantois and was immediately followed by 0.1 ml. of the suspension of the infecting organism. The necessary controls with saline solution and normal serum were included in each test. The relative susceptibility of chick embryos, hatched chicks and white mice was determined by the subcutaneous or chorioallantoic injection of known numbers of organisms.

EXPERIMENTAL RESULTS

When 12-day chick embryos were inoculated with graded doses containing from about 20 million to about 200 million plague bacilli, fairly striking differences were observed between the survival time and the hatching of chicks given virulent and those given avirulent *P. pestis*. A summary of the results obtained in several such experiments is presented in Table I. While there is no difference in the survival time of chick embryos infected with 200 million virulent or avirulent organisms, doses of 1 million organisms or less permit a significantly longer survival of chicks given avirulent bacilli. With doses of 5,000 or less avirulent *P. pestis* a few of the injected chicks regularly survived the infection and hatched at term. The percentage of hatching was never very large, but with such small numbers of avirulent bacilli (20 to 2,000) the average survival time of 12-day-old chicks was increased to almost 8 days after inoculation, since many of the animals died while hatching. Equally small numbers of virulent bacilli killed all chicks with an average survival time of 3.2 to 4.8 days.

The ability of avirulent *P. pestis* to persist and multiply in chick embryos without causing the latter's death was further investigated by killing chicks that hatched after infection with avirulent bacilli, and culturing their organisms. Some of the more important results obtained are presented in Table II. It was found that the number of bacilli in the infecting dose which permitted hatching of a significant proportion of chick embryos varied greatly with the route of administration and with the age of the embryo. Embryos less than 11 days old were quite highly susceptible and permitted the extensive multiplication of avirulent organisms leading to toxemia and death. Embryos of more than

TABLE I

Average Length of Life of Chick Embryos Infected with Equal Numbers of Virulent or Avirulent P. pestis

Approximate no. of organisms in infective dose	No. of 12-day chick embryos infected in each group	Average length of life* in days following inoculation with			
		Avirulent bacilli		Virulent bacilli	
		Days	% of embryos hatching	Days	% of embryos hatching
1 "loopful"	12	2.8	0	2.0	0
200 million	12	2.6	0	2.6	0
20 million	24	3.9	0	2.3	0
4 million	30	3.8	0	2.6	0
200 thousand	35	5.8	0	2.4	0
2 thousand	60	7.4	15	3.2	0
200	40	8.9	25	3.7	0
20	40	8.5	30	4.8	0

* Length of life of hatching chicks calculated as 11 days. Most of the dead embryos and some of the hatched chicks gave positive cultures when liver material was plated.

12 days' incubation usually died from large numbers of avirulent *P. pestis* but did not permit the survival of small numbers, so that no organisms could be recovered from the hatched chicks. Administration of the infecting dose on the chorioallantoic membrane or into the allantoic space was survived by some 12-day chicks only if less than 5,000 avirulent bacilli were given. Injection into the yolk sac, on the other hand, permitted the use of 500,000 avirulent *P. pestis* without unduly high mortality. The data presented in Table II were thus obtained under optimal conditions of infective dose (maximal) and age of chick embryos. It could be demonstrated that avirulent bacilli survive under suitable conditions for 3 days, on rare occasions for 4 days, after hatching of the chick, and can be recovered from the liver by simple culturing on blood agar plates and in gentian violet enrichment broth.¹ In spite of numerous attempts it was not possible to recover avirulent plague organisms after more than 4 days following hatching. This uniform disappearance of avirulent organisms around the fifth day after hatching suggested that a host-factor might be re-

TABLE II
Latent Infections in Chick Embryos Injected with Avirulent P. Pestis (Strain A1122) by Several Routes

Route of administration	Number of organisms administered	Number of chick embryos injected	Age of embryos in days when injected	Hatching		Plague organisms recovered from liver	
				Number	Per cent of total	Killed on day after hatching	Number positive over total number tested
Chorioallantoic membrane	3,000	38	14	10	26.3	1	6/10
Chorioallantoic membrane	3,000	83	12	17	20.5	3 4 5	3/8 2/6 0/3
Yolk sac	300,000	43	12	16	37.2	2 3 5	7/8 2/4 0/4
Allantoic space	3,000	35	14	8	22.8	3 4	1/6 0/2
Allantoic space	300	30	13	8	26.6	2 3	2/5 0/3

sponsible which was not present in a significant degree previous to that time. Such a host-factor might be evidenced by a high degree of resistance developing about the time of hatching. The susceptibility of 14-day chick embryos was therefore compared with that of newly hatched chicks, both with regard to infection with virulent organisms and to toxic extracts derived from *P. pestis*.² In several experiments it was found that 24 hours after hatching chicks were approximately one million times as resistant to infection with virulent or avirulent bacilli as 14-day-old chick embryos and that they withstood at least 10 mouse minimal lethal doses of toxic extract, i.e., at least 100 chick embryo minimal lethal doses. The resistance of 24-hour-old chicks to infection was also spectacularly greater than that of mice, 30 million virulent organisms being necessary to kill all animals in a group upon subcutaneous injection. When avirulent strain A1122 was administered subcutaneously in doses of 100 million bacilli to groups of 1-day-old chicks, none of the animals died, and plague organisms could be recovered up

to the third day, only from the local lesions, but never from the liver. These findings were interpreted as probably indicative of the activation of a cellular mechanism a few days previous to, or at the time of, hatching.

There is reason to believe⁷ that the action of antiplague serum in mouse protection tests depends, in part at least, upon the presence of a cellular mechanism that can be specifically activated. If such a mechanism were absent from 12-day chick embryos, then it could be predicted that immune serum of proved protective quality for mice should be without effect in chick embryos. This hypothesis was put

TABLE III
Serum Protection Tests in Chicks

Strain		Number of organisms	0.1 cc. saline or antiserum dilution 1:2	Number hatching over total number in group	Average life in days after inoculation	Remarks
13-day chicks	106	3,000	Saline	0/12	5.7	With 106 in chicks the membranes were positive and livers positive
	106	3,000	Serum	1/12	7.9	
	A1122	300,000	Saline	3/12	7.3	With A1122 in some chicks the membrane was positive and liver negative, especially in those dying later
	A1122	3,000,000	Serum	4/12	7.6	
	A1122	3,000,000	Normal rabbit serum	2/10	7.9	Of 10 hatched chicks only 6 survived 48 hours; of these 6, 4 were positive at 48 hours after hatching
11-day chicks	A1122	3,000,000	Saline	0/17	2.7	All membranes and livers positive; most spleens positive
	A1122	3,000,000	Serum	0/16	5.1	
	106	30,000	Saline	0/17	2.0	
	106	30,000	Serum	0/17	3.1	

to test by inoculating 1 or 10 minimal lethal doses of virulent or avirulent organisms on the chorioallantoic membrane together with 2 provisional standard units of antiplague serum. Half this amount of serum will, on the average, protect mice against a lethal *P. pestis* infection as used in a standardized serum protection test.⁷ The results of two such experiments are given in Table III. There was a slight increase in average survival time of serum-treated chick embryos over nontreated chick embryos, but it was statistically not significant in larger series. The occasionally observed longer survival time of serum-treated chick embryos infected with avirulent bacilli may possibly be due to the antitoxic properties of the serum. It is believed that these results tend

to confirm the concept of the absence of a significant cellular defense in the 12-day embryo and its appearance around the time of hatching.

GROSS AND MICROSCOPIC OBSERVATIONS OF PATHOLOGIC CHANGES

The chorioallantoic membrane of 12-day-old chicks inoculated with 10,000 to 500,000 organisms of avirulent or virulent *P. pestis* showed the following changes: 24 to 48 hours following inoculation the membrane appeared edematous, and sometimes pin-point hemorrhages could be seen. These hemorrhages were much more pronounced after 60 hours if virulent organisms had been used for inoculation, and progressed steadily until death on the third to fourth day. With avirulent bacilli there were usually no hemorrhages to be seen from the third day on, but pock-like lesions appeared on the membrane which had a tendency to coalesce and form a marked central thickening. This elevation assumed first a whitish opacity, later a yellow coloring, and increased in firmness and height until either death or hatching. Its center frequently showed ulceration after the fifth day following inoculation of the chick embryo. Similar changes were seen if very small numbers of virulent bacilli were dropped on the chorioallantois, but with larger numbers (more than 5,000) the extensive hemorrhage dominated the picture and death usually occurred too soon for any proliferative changes to be noticed. In these cases the embryo also exhibited very marked subcutaneous hemorrhage, particularly on the head and neck, but the internal organs were only little involved, showing but slight enlargement, bright red color and no necroses. The visceral changes were altogether negligible in embryos inoculated with avirulent *P. pestis*. Even though it was possible to recover viable plague bacilli from spleen and liver of a number of embryos, these organs gave no microscopic evidence for reactive changes.

Comparative microscopic observations were carried out on several series of chick embryos (12 days old) inoculated on the chorioallantois with 30 or 300 plague bacilli. Control series injected with saline solution only provided the standard for comparison. Twelve-day embryos given about 30 virulent *P. pestis* organisms survived for 4 to 8 days. Twenty-four hours after inoculation the chorioallantoic membrane appeared slightly edematous, the capillary plexus seemed engorged and the ectodermal epithelium was proliferating slightly. There was no significant cellular reaction to be seen in the mesoderm. Liver and spleen appeared somewhat hyperemic. On the second day after inoculation the ectodermal proliferation had not progressed but the mesodermal edema was increased and there was some perivascular accumulation of large mononuclear cells. In a few places on the membrane extra-

sation of erythrocytes could be noticed. The liver and spleen were unchanged. On the third day after injection bacilli could be observed microscopically for the first time. Some were seen within ectodermal cells of the epithelium which was not significantly hyperplastic, others between cells. Few only could be detected in the mesoderm within phagocytes or free. There were many mononuclear cells in the mesoderm, singly or in small groups, and particularly in perivascular "cuffing." On the fifth day after inoculation the membrane gave a picture of maximal edema with very intense cellular infiltration and large masses of bacilli throughout the basal regions of the mesoderm. In the upper layers of the mesoderm, in the vicinity of the capillary plexus, small heaps of bacilli were seen surrounded by densely packed mononuclear cells forming micro-abscesses. Few organisms, only, could be located definitely within phagocytes. There was very extensive multiplication of *P. pestis* in the liver, associated with cellular degeneration evidenced by loss of nuclear staining properties and slight vacuolization of some lobular margins. Relatively few mononuclear cells had infiltrated the liver sinusoids and the lymphocytic proliferation in the spleen was very moderate. In contrast to the finding of Buddingh and Womack,³ however, the spleen was definitely the site of quite extensive focal bacterial localization and multiplication.

A similar series of eggs inoculated with about 300 virulent *P. pestis* organisms showed an identical sequence of events. All eggs in both of these series gave positive cultural results from the chorioallantoic membrane, and organisms could also be recovered from the livers of most of the embryos.

The inoculation of similarly small numbers of avirulent plague bacilli did not result in such histologic changes as just described for virulent bacilli. Most of the chick embryos survived until hatching term, following administration of 30 to 300 avirulent organisms on the chorioallantoic membrane, and about 30 per cent actually hatched while the rest were too weak to escape from the shell. Although it was possible to recover avirulent plague organisms from such chick embryos (from the chorioallantoic membrane and the liver) even 8 and 10 days after inoculation, histologic sections were almost indistinguishable from those prepared from an uninoculated control series. In a few instances there was a slight ectodermal proliferation and some monocytes could be seen in the mesoderm, but it was never possible to definitely identify bacilli in the sections and the reactive changes in either membrane or chick organs did not reach a significant level. Since the use of large avirulent inocula (about 1 million organisms) produces lesions in the chick embryo which resemble in all details those caused by small num-

bers of virulent bacilli, as previously described, the failure of small avirulent inocula to induce pathologic changes must be ascribed to their extremely slow rate of multiplication.

Histologic studies were also performed on chick embryos used for serum protection tests, mentioned previously. The reactions induced by 30,000 virulent organisms in 11-day-old chicks were fairly similar and varied but insignificantly with the treatment with saline solution or serum. After inoculation of either virulent or avirulent organisms and treatment with saline solution, the following changes could be observed regularly on the second or third day: The ectodermal epithelium was slightly hyperplastic and only a few bacilli could be seen in and between epithelial cells. The mesoderm appeared moderately edematous and its vessels engorged. There were a few small clumps of bacilli in the region of the capillary plexus but beneath it a solid mass of organisms extended through the deeper parts of the mesoderm. The inflammatory reaction to this bacterial invasion was negligible, with the appearance of only very few scattered mononuclear cells. A small number of bacilli were present in the liver without causing significant degenerative or inflammatory changes. In the case of chick embryos treated with hyperimmune antiplague serum before inoculation with avirulent organisms, the final picture was similar to that seen in nontreated chicks except for more extensive edema of the mesoderm, definite ulceration of the epithelium, and more pronounced mononuclear cell infiltration in membrane and liver. A number of serum-treated chicks dead on the second and third day after avirulent inoculation gave evidence for only limited bacterial invasion and multiplication. Death in these animals probably occurred due to the pronounced toxin sensitivity and a considerable amount of toxin liberated from the large inoculum after only slight multiplication. Serum-treated chicks given a virulent inoculum of 30,000 organisms did not differ from the untreated controls in any respect.

DISCUSSION

It has not been possible up to the present time to distinguish virulent from avirulent *P. pestis* by means of serologic tests.⁸ This may indicate either that there is actually no difference in antigenic make-up between these types of bacilli or that such a difference has as yet escaped detection. It was proposed recently² that the dissociation of virulent into avirulent plague bacilli may take place through a loss of antigenic constituent, chemical group, or property that either does not contribute to the exterior of the organism and thus would be difficult to determine, or may be highly unstable and easily destroyed. It

has been shown¹ that avirulent bacilli are to some extent invasive, pathogenic and toxic, so that these criteria are of no value for their differentiation from virulent organisms. No significant difference could be detected⁹ between virulent and avirulent strains of *P. pestis* in either experiments evaluating coagulase and fibrinolysin activities or phagocytosis tests with artificially induced exudate. It appears, therefore, that the only striking characteristic that separates virulent from avirulent bacilli is the inability of the latter to proliferate freely, even in a highly susceptible or severely intoxicated host.¹ The results reported in this paper support such a view, for small numbers of avirulent organisms failed to give any evidence for significant multiplication in the highly susceptible chick embryo, while equally small inocula of virulent organisms multiplied extensively in a short time. This might be interpreted as indicating that avirulence may be a function of the loss of certain cellular enzyme systems which permit abundant multiplication in the animal host. It seems to be largely independent of the animal's defense mechanism, for studies^{1,7} have shown that the effect of the immune animal or of exudative phagocytes mixed with immune serum is practically the same on virulent and avirulent plague bacilli. Furthermore, the 12-day-old chick embryo appears to be largely devoid of an efficient defense mechanism; nevertheless, the avirulent bacilli introduced in relatively small numbers do not proliferate freely. They do, however, persist until hatching time of the chick and sometimes even a few days longer, until the quickly developing defensive mechanism of the hatched animal disposes of them. This latent infection is somewhat similar to that reported by Oag¹⁰ for *Borrelia duttoni*. Hatched chicks are extremely resistant to both intoxication and infection with *Pasteurella pestis* and are practically immune to the spirochete. Chick embryos are highly susceptible to both microorganisms and it appears that resistance develops rather suddenly upon hatching. The immaturity of the defensive mechanism in the chick is evidenced also by the fact that antisera of high protective value for mice are unable to protect embryos against plague infection. Furthermore, the histologic studies gave evidence for the low degree of defense, in the form of inflammatory response to plague infection, usually obtained in embryos.

In accordance with the findings in other experimental animals,¹ it was shown again that avirulent *P. pestis* inoculated in sufficiently large numbers can produce an invasion similar in all respects to that caused by virulent ones. The histologic observations made on eggs given small inocula of *P. pestis* emphasize the invasive features but fail to show the extensive ectodermal proliferation and destruction observed by

Buddingh and Womack³ upon inoculation of "a loopful" of culture. This destruction as well as the "profuse hemorrhage" and "marked injury to the vessels" most likely is due to the toxic impact of the large bacterial mass and does not occur if smaller, primarily nontoxic doses of organisms are used. The blood stream invasion of the embryo regularly led to the development of foci not only in the liver³ but also in the spleen, both organs filtering plague bacilli out of the blood coming from the chorioallantoic membrane. The reaction of the embryo is approximately the same to equal large doses of virulent and avirulent *P. pestis* so that a histologic differentiation is impossible. It appears probable that the final criterion of virulence will have to rest on a biologic and chemical identification of the bacterial enzyme systems which are responsible for multiplication of plague bacilli in the animal host.

SUMMARY AND CONCLUSIONS

1. Chick embryos of 12 to 14 days' incubation are very highly susceptible to infection with *P. pestis*. Twenty virulent, or 200,000 avirulent plague organisms bring about death of the embryos in 4 to 8 days. In spite of this high susceptibility, avirulent plague bacilli inoculated in small numbers fail to proliferate freely. The lack of abundant multiplication even in a highly susceptible host is considered an inherent characteristic of completely avirulent *P. pestis* organisms.

2. Avirulent plague bacilli administered onto the chorioallantoic membrane of 12-day-old chick embryos in sublethal doses persist in the embryo's organs until hatching time and sometimes for 3 to 4 days after hatching of the chick.

3. Newly hatched chicks are very highly resistant to plague infection and large doses of virulent organisms are disposed of rapidly, probably through the agency of a cellular mechanism that is activated at hatching time. The absence of such a mechanism in 12 to 14-day-old chick embryos may be responsible for their high susceptibility.

4. Hyperimmune plague antiserum of known protective quality for mice is unable to protect chick embryos against an infective dose of *P. pestis*. This is taken to indicate that a cellular defense mechanism must be present for antiserum to exert its protective action. In the absence of such a mechanism only the antitoxic, but not the anti-infectious, activity of antiserum becomes evident.

5. Histologic observations indicate that virulent *P. pestis* are distributed from the membrane by way of the blood stream to all organs of the embryo and produce in them degenerative lesions. The proliferative response to either virulent or avirulent plague bacilli in the embryo's organs appears slight. Ulceration of the ectoderm and vas-

cular damage occurs only when very large inocula are used and is an expression of toxic action.

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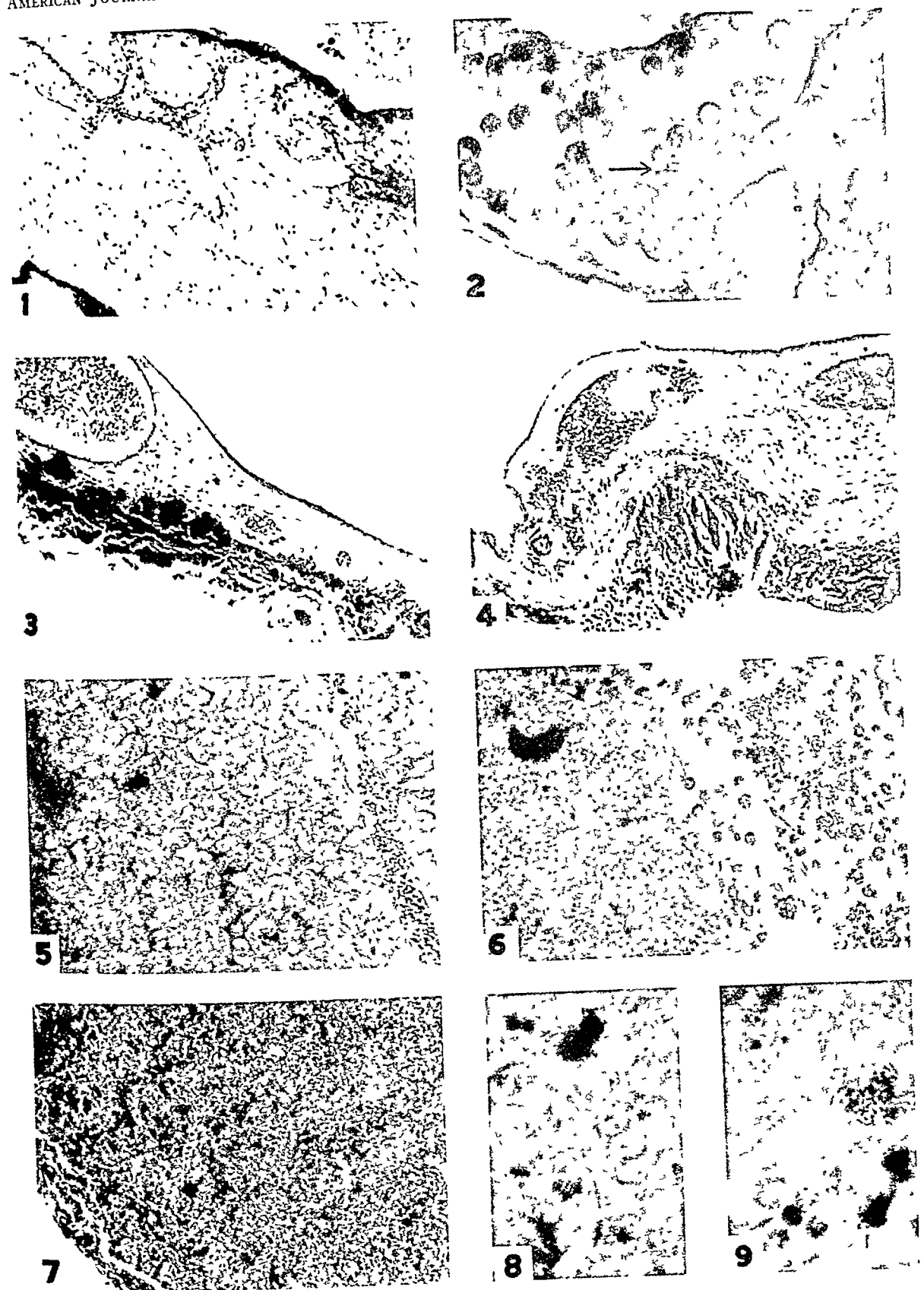
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[Illustrations follow]

DESCRIPTION OF PLATE

PLATE 87

- FIG. 1. Chorioallantoic membrane from a 15-day-old chick embryo, inoculated on the 12th day with about 30 virulent *Pasteurella pestis* organisms. There is very slight ectodermal proliferation but marked mesodermal edema. Giemsa's stain. $\times 70$.
- FIG. 2. Detail from Figure 1 showing a small cluster of plague bacilli in the mesoderm of the membrane, with some mononuclear cells. Giemsa's stain. $\times 635$.
- FIG. 3. Chorioallantoic membrane from a 14-day-old chick embryo, inoculated on the 11th day with 30,000 virulent plague bacilli. There is no significant proliferation of the ectoderm and but negligible mesodermal edema, but there has been massive multiplication of organisms in the basal parts of the mesoderm. All vessels are engorged. Giemsa's stain. $\times 20$.
- FIG. 4. Membrane from a chick embryo treated similarly to that shown in Figure 3, but given in addition hyperimmune plague antiserum simultaneously with the infective dose. More marked edema than shown in Figure 3, intense hyperemia, and massive bacterial proliferation in the basal regions of the mesoderm are present. Giemsa's stain. $\times 20$.
- FIG. 5. Liver from the same chick embryo as that shown in Figure 3. Focal bacterial proliferation and slight degenerative changes are seen in the lobules adjoining such foci. Giemsa's stain. $\times 70$.
- FIG. 6. Detail from Figure 5, showing a focus of bacterial multiplication in the liver parenchyma and simultaneous intravascular proliferation. Giemsa's stain. $\times 320$.
- FIG. 7. Spleen from the same chick embryo as that shown in Figure 3. Several foci of bacterial multiplication are shown in the pulp. Giemsa's stain. $\times 70$.
- FIG. 8. Detail from Figure 7, showing one small mass of multiplying organisms in the splenic pulp and a number of single organisms both intercellular and intracellular. Giemsa's stain. $\times 635$.
- FIG. 9. Detail from Figure 5. Bacteria are carried by the blood stream, free and in white cells. One clump of multiplying organisms adheres to the endothelium of a hepatic vein. Giemsa's stain. $\times 635$.



Jawetz and Meyer

Pasteurella pestis in the Chick Embryo

THE PATHOLOGY OF FATAL EPIDEMIC HEPATITIS *

BALDUIN LUCKÉ, Lt. Col., M.C.

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INTRODUCTION

During the spring and summer of 1942 an outbreak of jaundice of considerable magnitude occurred in the Army of the United States. General information concerning this outbreak has been given by the Surgeon General in a circular letter which was published in medical journals.¹ As stated in this circular, groups of investigators were assigned the study of various aspects of the disease; investigation of its pathology was conducted in the laboratories of the Army Medical Museum, where material from all available sources was assembled. This paper is based upon a study of 125 cases; the patients included

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the military personnel and, in addition, a number of civilians who died during the outbreak. The contents and arrangement of the paper are given above. The study does not include a consideration of the etiology, nor of the clinical manifestations of nonfatal cases; these aspects are dealt with by others,²⁻⁴ in reports in which the relation of the administration of yellow fever vaccine, containing human serum, to the outbreak of hepatitis and jaundice are considered in detail.

Historical

Epidemics of Hepatitis. The disease which is variously known as epidemic hepatitis, infective or infectious hepatitis, or epidemic catarrhal jaundice is not new. Outbreaks with similar clinical and pathologic manifestations have occurred for at least the past 100 years.⁵⁻⁸

The disease has always been prevalent in armies, and particularly so in times of war. Hence English writers have referred to it as camp jaundice, or epidemic catarrhal jaundice of campaigns,⁹ French writers as "jaunisse de champs,"¹⁰ German writers as a "Kriegs" icterus catarrhalis, or "Soldatenkrankheit" icterus.^{11, 12}

One of the largest of recorded epidemics occurred in this country during the Civil War.¹³ During the first year there were 10,922 cases with 40 deaths among the Federal troops (the mean strength of the U. S. Army being 279,371 men). During the second year 32,154 cases occurred with 119 deaths (mean strength of Army, 614,325 men). During the third year the epidemic declined; there were 9057 cases and 67 deaths (mean strength, 619,703). In the fourth year the number of cases had fallen to 294 with 5 deaths (mean strength of Army, 89,143). Woodward¹⁴ in his book on "Outlines of the Chief Camp Diseases of the U. S. Armies," published in 1863, gives an excellent account of the clinical course of the disease.

"When this form of jaundice attacks a regiment or an Army, it usually appears in a number of cases simultaneously or in close succession like other epidemic disorders, lasts in each case from one to six weeks, or even longer, and then slowly disappears. The appearance of the icteroid hue is, as a rule, preceded by more or less derangement of the general health; sometimes, however, only by a few days of headache, constipation, and malaise, and occasionally the discoloration of conjunctiva and skin is the first noticeable symptom. The color of the skin may vary from a scarcely noticeable tinge to a deep tawny-orange color; this condition is accompanied by depressed spirits, intellectual torpor, loss of appetite, general debility, and uneasy sensations over the region of the liver and the stomach. Hepatic tenderness is a very variable symptom; enlargement of the liver, as indicated by an increased area of dullness on percussion, is more common. Sometimes there is nausea and vomiting. The stools are usually clay colored, and the bowels constipated, though at times there is diarrhoea. The urine is discolored from the presence of biliary matters. Very often the patient is so debilitated as to be quite unfit for duty, though not usually confined to his bed; at other times, however, he continues to perform service throughout the affection.

"After lasting a variable period, the symptoms slowly subside and the patient is gradually restored to health, the mental torpor and debility persisting often some time after the icteroid hue has disappeared. The first symptom of amendment is generally a change in the color of the stools, which gradually resume their normal appearance. Cases occasionally occur of a graver character than indicated above, the symptoms of biliary toxemia being aggravated to stupor or even coma, and such cases at times prove fatal."

This description of the epidemic of 1862 gives a good picture of the epidemic of 1942. Indeed, with minor variations, the clinical manifestations in the many epidemics have been remarkably similar.

During the Franco-Prussian War there were 2344 cases in the Prussian Army, 1311 cases in the Bavarian and 407 cases in the Saxon Army.^{15, 16} During the South African War 5,648 cases were recorded.¹⁰ In World War I, epidemics occurred in the armies of several nations. Among the British, so-called catarrhal jaundice first broke out in July, 1915, among troops stationed in Egypt; thereafter the epidemic spread rapidly to Gallipoli, where 2195 cases occurred from September to November, and then to Mesopotamia, where 1538 British and 2634 Indian troops were affected.^{9, 17} The disease was as frequent among the French as among the British, but no cases occurred among the Turks. Among Rumanian troops there was a serious epidemic in the fall of 1917; one writer speaks of it as taking place in an almost explosive manner. Several thousand men were affected.¹⁸ (See this paper for references to outbreaks among German troops.) No noteworthy epidemic occurred in the American Army during the war, but a relatively small outbreak developed in the Army of Occupation.¹⁹

Since the war, epidemic hepatitis has become widely prevalent among the populations of several countries. Blumer²⁰ recorded many outbreaks in the United States, of which more than 200 were observed during 1921 and 1922 in the State of New York alone. Cullinan²¹ gave a list of reported outbreaks between 1926 and 1939 in England. Ruge²² recorded an extraordinary rise in incidence of hepatitis between 1919 and 1929 in the German Navy. But it is in the Scandinavian countries that the disease became especially widespread and virulent. The extensive literature dealing with these Scandinavian epidemics is collected in the papers by Ehrström,²³ Wallgren,²⁴ Wickström²⁵ and Selander.²⁶

In the present War, as in previous wars, the disease has at times been prevalent in the combatant forces: in the Army of the United States,¹ in British Forces^{27, 28} and in the German Army.^{12, 29, 30} In discussing the occurrence of hepatitis in the German Army, Dietrich,¹² in 1942, stated that it had become one of the most important epidemic diseases.

Terminology. Until recent years, the disease under consideration was universally spoken of as catarrhal jaundice. This term reflected the views of Virchow³¹ concerning its pathogenesis and nature. He believed that catarrhal jaundice is caused by inflammatory swelling of the orifice of the common bile duct, which, he thought, became obstructed by a plug of mucus and desquamated epithelium. Although he gave detailed directions for opening the duct so as to observe the occluding plug, the reader of his paper is left in doubt how often Virchow observed such an obstruction. In the course of time the correctness of Virchow's view was questioned by many clinicians; and the hypothesis was proposed that the site of the essential lesion is not in the extrahepatic bile ducts but in the liver.³² So-called catarrhal jaundice gradually came to be regarded as an inflammatory process in the liver itself, *i.e.*, a form of hepatitis.

The term "epidemic hepatitis" was first applied by Lindstedt³³ in 1918 to the epidemic form of "catarrhal jaundice"; he proposed this term in contradistinction to "infectious hepatitis" or Weil's disease. Lindstedt's nomenclature has been followed particularly in the Scandinavian countries and on the European continent. In the United States and in Great Britain various terms are in use: infective jaundice, catarrhal jaundice, so-called catarrhal jaundice, infectious hepatitis, infective hepatitis, simple hepatitis, and epidemic hepatitis. None of these terms is wholly satisfactory. Probably not until the discovery of its etiologic agent will the disease receive a definitive name. In this paper, following the rules of priority in nomenclature, the disease will be referred to as epidemic hepatitis.

The Relation Between the Sporadic (Endemic) and the Epidemic Form of Hepatitis. It is the consensus at present that epidemic hepatitis is the epidemic form of the disease which in sporadic cases has hitherto been called catarrhal jaundice.^{7, 24-26} The sporadic and epidemic forms are related in somewhat the same way as are sporadic and epidemic poliomyelitis or influenza.^{5, 7} Many epidemics of hepatitis have been traced to sporadic cases, and the two forms cannot be distinguished on either clinical or epidemiologic grounds.⁷

Not every student of this disease, however, shares the view that the two forms are identical. Thus Selander²⁶ in his recent monograph stated that although the two forms have a very similar clinical picture, he yet considers sporadic catarrhal jaundice and epidemic hepatitis as two different diseases. He based his opinion on the more gradual development of the sporadic disease, which tends to affect adults, whereas the more rapidly developing epidemic form tends to affect children. Dietrich,¹² on the other hand, came to the conclusion that any differences in development or course merely represent reactions at two dif-

ferent age periods. All investigators agree that the question cannot be settled conclusively until the etiology of epidemic hepatitis is established.

Mortality. Like the sporadic form, epidemic hepatitis usually runs a mild course. The mortality is low; the rates in various epidemics, including the outbreak of 1942, have ranged from 0.13 to 0.44 per cent. During the Civil War there were 52,429 reported cases of jaundice and 231 deaths, with a mortality rate of 0.44 per cent.¹³ During the previous World War, 1538 British and 2634 Indian troops stationed in Mesopotamia were affected, with a mortality of 0.4 per cent.¹⁷ The incidence in the German Navy between 1919 and 1929 was approximately 2500, with a mortality of 0.13 per cent.²² During a large epidemic in Finland, between 1933 and 1936, the mortality was 0.34 per cent.²⁴ Selander²⁶ estimated the mortality in recent Swedish epidemics as from 0.2 to 0.4 per cent.

In conformity with the policies of the War Department, specific statements concerning numbers of cases must for the present be omitted. It is possible, however, to state that in the 1942 outbreak the mortality was 0.24 per cent, *i.e.*, even lower than in most other recorded epidemics.

Pathology. Until the previous World War there was no precise information as to the lesions of catarrhal jaundice. During the war Eppinger³⁴ performed autopsies on three soldiers who died of trauma. The liver showed lesions which he regarded as a miniature form of acute yellow atrophy. For the first time it was shown by morphologic examination that catarrhal jaundice is in fact a disease of the liver. There was no obstruction of the extrahepatic biliary passages.

There have been but few other post-mortem examinations; a case was reported by Klemperer, Killian and Heyd,³⁵ one by Gaskell,³⁶ another by Schrumpf,³⁷ one by Barber and Osborn.³⁸ All confirmed Eppinger's findings that catarrhal jaundice is a disease which causes destructive changes in the liver.

To this meager information much has been added by the studies of Roholm and Iversen³⁹ and by those of Dible, McMichael and Sherlock.⁴⁰ These investigators examined material obtained for biopsy by aspiration of the liver during various stages of the disease. It became certain that catarrhal jaundice is a form of hepatitis.

Relation of Epidemic Hepatitis (Catarrhal Jaundice) to Idiopathic Yellow Atrophy. The studies previously mentioned deal with the lesion occurring in the usually benign, nonfatal case. During large epidemics, when perhaps the disease becomes more virulent, a much greater number of patients have been examined post-mortem. Invariably, the liver has shown the changes of idiopathic yellow atrophy. As early as 1912

Cockayne⁵ reviewed the evidence for linking these two diseases which generally had been regarded as unrelated. He came to the conclusion that catarrhal jaundice and yellow atrophy are usually due to the same cause, a specific organism of unknown nature. Since the last war, many observers have commented on the increasing frequency of catarrhal jaundice, in both its sporadic and epidemic forms, and on the greater frequency with which acute yellow atrophy (not related to poisons or bacterial infection) has appeared at the autopsy table. Most of the cases of idiopathic yellow atrophy have occurred during or shortly following an epidemic of catarrhal jaundice. In the Scandinavian countries and in Great Britain both diseases seem to have been more prevalent than elsewhere; and in these countries many investigators have taken the view that yellow atrophy and benign catarrhal jaundice are but two extremes of one and the same disease.^{5, 7}

This view is not shared by all investigators. During the serious outbreak of hepatitis in Sweden during 1927, Bergstrand⁴¹ studied 95 fatal cases. Yellow atrophy of the liver was found in all. He regarded yellow atrophy merely as a complication of epidemic hepatitis. Bergstrand gave no adequate grounds for making this distinction, and his views were not generally accepted.

During the present war, several papers have dealt with the pathology of fatal epidemic hepatitis: Fox, Manso, Penna and Madureira Pará⁴² reported 17 cases from Brazil, Cameron²⁷ reported 4 fatal cases from Palestine, and Siegmund³⁰ 3 from Germany. Yellow atrophy of the liver was the common finding in all.

The present study supports the view that idiopathic yellow atrophy represents the extreme lesion of epidemic hepatitis. It remains to be emphasized that this form of yellow atrophy differs anatomically from the yellow atrophies caused by arsenic, phosphorus and a large number of other chemical agents. It also differs from the yellow atrophy of eclampsia, and that of a number of bacterial infections, particularly those involving the peritoneum.

Material and Methods

The material available comprised clinical records, autopsy protocols and fixed tissues from 125 cases. In approximately two-thirds of the cases the complete clinical data were examined; in the remainder, more or less complete abstracts of the records. All cases had been studied in hospitals, and all had been diagnosed clinically as epidemic hepatitis (or as epidemic catarrhal jaundice). Most of the post-mortem examinations were performed by Army Medical Officers; their cooperation has greatly facilitated this study.

Paraffin sections were prepared from all tissues, and those of the liver were stained with hematoxylin and eosin, by the Masson-Mallory method for connective tissue and by Wilder's method for reticulum. In many instances various fat stains were used, and the Giemsa and the MacCallum stain for bacteria. Sections of organs other than liver were usually stained with hematoxylin and eosin, and frequently by the other methods. Frozen sections of the brain in selected cases were stained by Cajal's gold sublimate method and by Hortega's method for glia; Nissl stains, hematoxylin and eosin and myelin stains were used for paraffin sections.

CLINICAL COURSE OF FATAL EPIDEMIC HEPATITIS

Epidemic hepatitis usually is a mild disease; its clinical course is well known and has been described in numerous papers. There is much less information concerning the course of hepatitis that terminates fatally. Therefore, in the present section an analysis is given of the clinical course of 125 fatal cases. In this analysis special emphasis is laid on the stages of the disease, on the times at which jaundice, ascites and nervous manifestations appeared, and on the more important laboratory findings. The data will be presented in the form of tables and graphs, so that only a brief summary need be given in the text. Abstracts of representative clinical records will be used to illustrate these data.

Age, Sex and Race of 125 Patients with Epidemic Hepatitis

The pertinent data are given in Table I. In the present series all except 4 patients were males; 94 per cent were whites, 6 per cent were colored. This distribution probably reflects the population in the Army, although no comparative figures are at present available. Seventy-

TABLE I
Age, Sex and Race of 125 Patients with Epidemic Hepatitis

Age (years)	Number of patients		
	White	Colored	Total
20-24	*46 (37%)	4 (3%)	50 (40%)
25-29	*45 (36%)	2 (2%)	47 (38%)
30-34	9 (7%)	0	9 (7%)
35-39	11 (9%)	1 (1%)	12 (10%)
40-44	5 (4%)	0	5 (4%)
45-49	0	0	0
50-54	2 (2%)	0	2 (2%)
Total	118 (94%)	7 (6%)	125

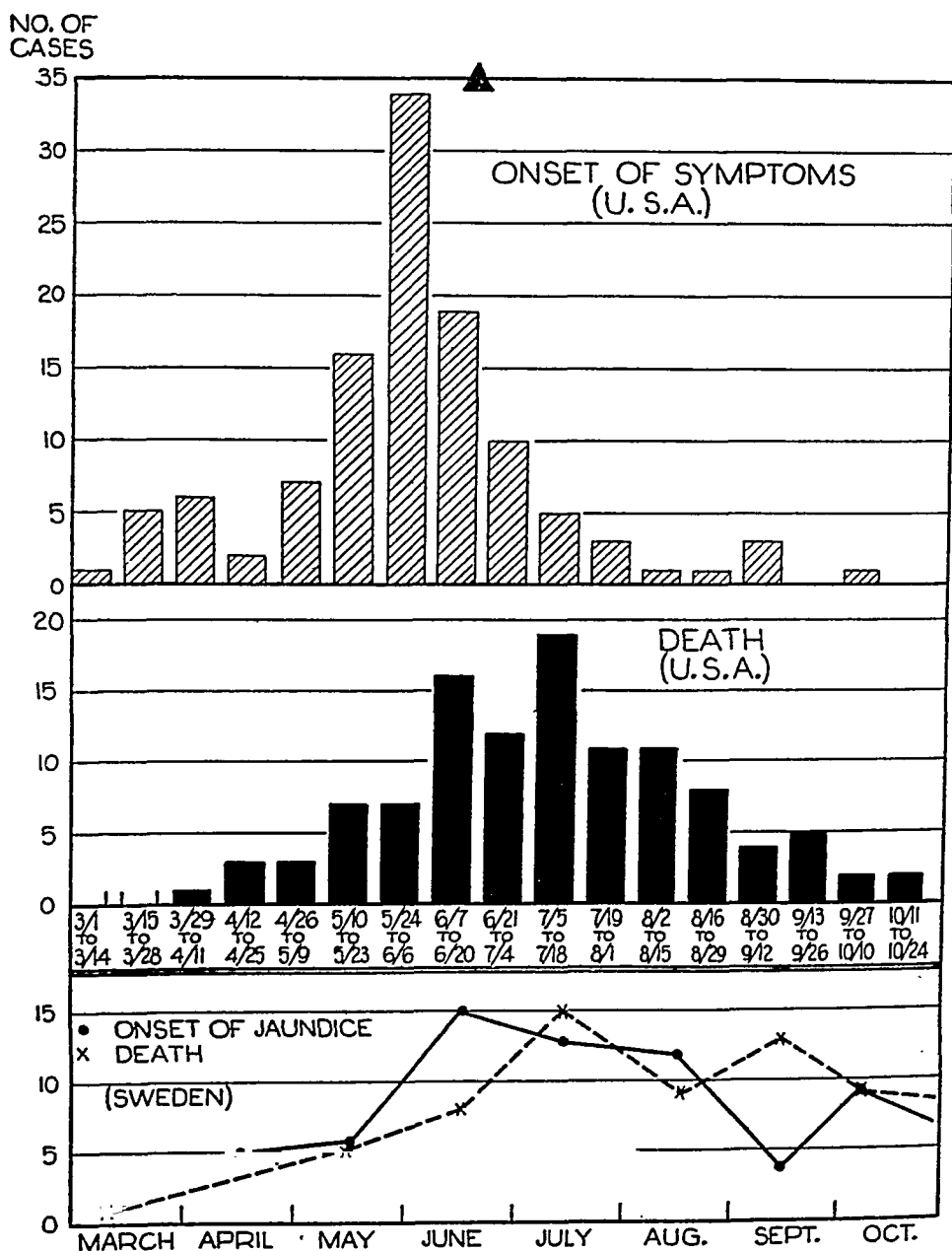
All except 4 patients were males.

* Includes 2 females.

eight per cent were below 30 years of age. It is of interest to point out that fatal epidemic hepatitis was not entirely confined to the younger age groups; 22 per cent of the patients were above the age of 30.

Relation of Season to Onset of Symptoms and Death

The outbreak of hepatitis began in March, reached its peak toward the end of June and thereafter gradually declined, so that by the end



Text-Figure 1

of August few new cases were developing. It seems of interest to compare the onset of symptoms and the time of death of the fatal cases, first, with those of the entire outbreak and, secondly, with those in the

great Swedish epidemic of 1927. These relations are shown graphically in Text-Figure 1. Here the onset of symptoms and the time of death have been graphed in bi-weekly periods. It will be seen that the peak of onset of symptoms in fatal cases (shown in upper part of the figure) corresponds closely with the peak for all the cases of the epidemic (this peak is indicated by a solid triangle on the top line of the graph).

The modes in these two graphs are approximately 4 to 6 weeks apart.

TABLE II
Duration of Disease in 118 Cases of Epidemic Hepatitis

Duration (days)	No. of cases	Per cent of cases
Less than 10	0	0
10-19	14	11
20-29	20	16
30-39	31	26
40-49	20	17
50-59	8	7
60-69	8	7
70-79	9	8
80-89	0	0
90-99	5	5
Over 100	3	3

That this length of time represents the most frequent duration of the disease is confirmed by the data given in Table II.

A similar relation between onset and time of death is shown for the Swedish epidemic at the bottom of Text-Figure 1.

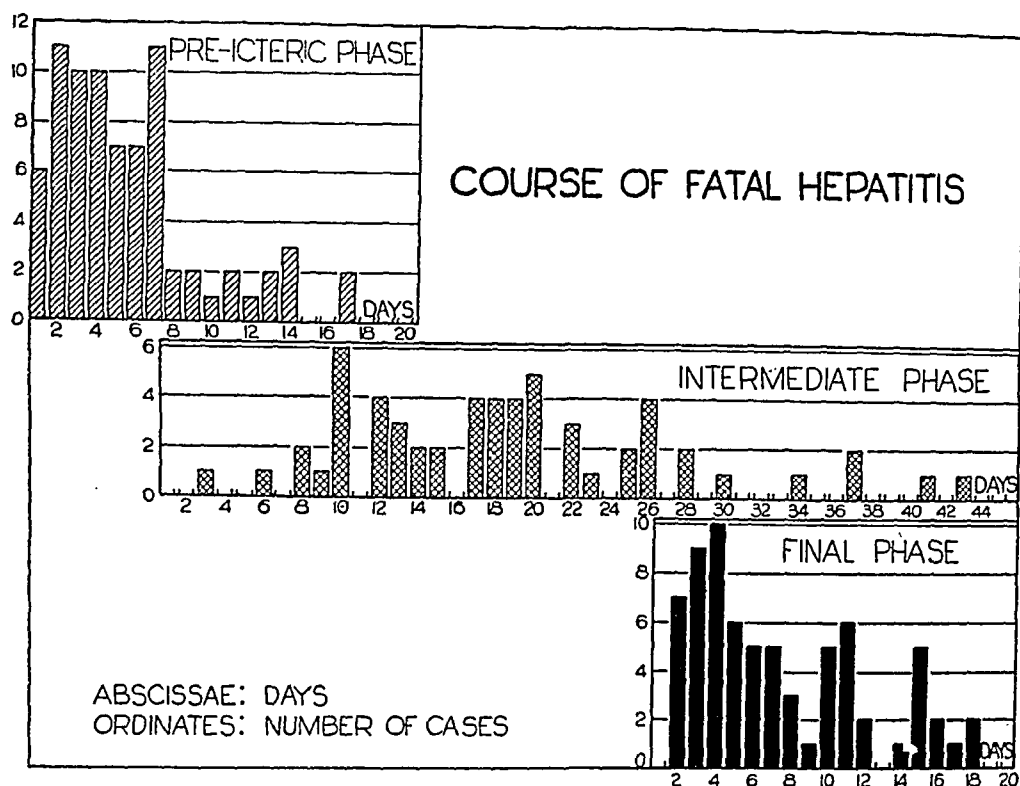
Course of Fatal Hepatitis

Three distinct phases in the clinical course of fatal hepatitis may be recognized: a pre-icteric, an intermediate and a final phase. The intermediate phase begins with the onset of jaundice and, in these fatal cases, usually ends abruptly with the appearance of new grave symptoms that presage the fatal termination. The time relation of the three phases is shown in a graph (Text-Fig. 2), where the ordinates give the number of cases, and the abscissae the duration. The pre-icteric phase in the great majority of cases lasted 7 days or less, and shows little scattering (see also Table III). In the intermediate phase, however, there is considerable scattering, though in the majority of cases the

TABLE III
Interval Between Onset of Symptoms and Appearance of Jaundice in 77 Cases of Epidemic Hepatitis

Interval (days)	No. of cases
1-4	37
5-9	29
10-14	9
15-19	2

duration was 26 days or less. The final phase, in the majority of cases, ran a course of 10 days or less.



Text-Figure 2

Initial Symptoms. The initial symptoms, *i.e.*, those of the pre-icteric stage, are presented in Table IV. The most common initial manifestations of the disease are anorexia, nausea, dark urine, abdominal

TABLE IV
Initial Symptoms in 120 Cases of Epidemic Hepatitis

Symptom	No. of cases	Per cent of cases
Anorexia	85	71
Nausea	62	52
Dark urine	39	33
Abdominal distress	37	31
Vomiting	29	24
Malaise	25	21
Weakness	24	20
Constipation	14	12
Headache	14	12
Fatigue	10	8
Backache	5	4
Coryza	3	3
Pruritus	3	3
Diarrhea	3	3
Chill	2	2
Urticaria	2	2
Epistaxis	1	1
Pain in joints	1	1
No pre-icteric symptoms	1	1

distress, vomiting, malaise and weakness. It should be emphasized that whereas approximately half the patients gave a history of nausea, only a quarter of the patients vomited.

Intermediate Phase. In the majority of cases the clinical picture in the intermediate phase gave no indication that the disease was not going to run the usual benign course. Many patients were ambulatory. In many instances the records contain statements such as "not acutely ill," "general condition good," "appears to be doing well," "uneventful course." In a considerable number the initial symptoms abated and the patients appeared to be steadily improving. Only in the exceptional case was the course grave from the beginning.

TABLE V
Duration of Final Phase in 73 Cases of Epidemic Hepatitis

Duration	No. of cases
(days)	
Up to 4	26
5-9	21
10-14	13
15-19	10
20 and over	3

Final Phase. A sudden dramatic change for the worse in 73 cases ushered in the final phase. The characteristic changes were nervous symptoms, ascites and persistent vomiting. The duration of this phase is shown in Table V. In over 60 per cent of the cases, death occurred within 10 days from the appearance of grave symptoms. Only 3 patients survived longer than 20 days (Table V).

Nervous Manifestations. In the great majority of cases the patients had signs of cerebral involvement. Particularly noteworthy were lethargy or coma, alternating with restlessness, excitement and delirium. Other manifestations were scanning speech, muscular weakness, and exaggeration of deep and superficial reflexes. Nervous manifestations usually ushered in the final phase; they marked the turning point. In a few cases, however, these manifestations appeared earlier or else were agonal (Table VI). The clinical course is illustrated by representative cases.

TABLE VI
Interval Between Onset of Nervous Manifestations and Death in 88 Cases of Epidemic Hepatitis

Interval	No. of cases	Per cent of cases
(days)		
Up to 4	53	60
5-9	19	22
10-14	8	9
15-19	6	7
20 and over	2	2

ILLUSTRATIVE CASES

Case 8

Clinical Course. The patient was a white male, 28 years old, who was well until the end of March, 1942. He then had anorexia, nausea and diarrhea; later, abdominal distress. On April 2, there was slight jaundice, but he was not ill and continued on duty until April 25, when he was admitted to hospital. Temperature, pulse and respiration were normal; liver enlarged, tender; urine, persistent traces of albumin and bile; stools, clay-colored. May 5: poor appetite; complained of being light-headed and dizzy; liver, enlarged and tender. May 8: slightly stuporous, somewhat confused. May 11: rapidly deepening stupor; sharp piercing cries; blood pressure, 150/85; disoriented and irrational; rapid change for the worse; alternating periods of coma and delirium. May 15: very toxic and delirious; did not respond to questions. May 16: comatose; rapid decline; vomited brownish material; died on this date.

Case 13

Clinical Course. The patient was a white male, 26 years old. On April 4, 1942, there was anorexia and later vomiting. April 9: jaundiced. Admitted on April 29, deeply jaundiced, tired, responsive; no fever; pulse, 76; abdomen flat; liver not palpable but slightly tender. May 5: temperature rose to 101° F.; blood pressure, 140/80; markedly dehydrated. May 6: somewhat stuporous; intermittent spasm of left sternocleidomastoid muscle; jerked head from side to side; tendon reflexes hyperactive but approximately equal on the two sides; sustained ankle clonus; Babinski reflex negative. May 17: abdomen distended; paracentesis, 600 cc. of fluid withdrawn. May 19: paracentesis, 1500 cc. of fluid withdrawn. May 21: paracentesis, 1500 cc. of fluid withdrawn. May 22: stupor progressed into coma. May 23: died.

Laboratory Findings.

Date	Color	Specific gravity	Urinalyses		Acetone	Sugar	Bile
			Albumin				
April 30	Dark	1.011	—			+	+
April 30	Coffee	1.015	+			—	+
May 1			—			—	+
May 2			+				++
May 5	Coffee	1.010	Faint trace		—	—	++
May 6							++

Blood Counts

Date	Red blood cells (millions)	White blood cells	Neutrophils (per cent)	Lymphocytes (per cent)	Monocytes (per cent)	Eosinophils (per cent)
April 30	4.85	9,300	59	27	2	1
May 1	5.48	7,200	60	23	12	2
May 4	5.62	7,450	48	42	9	
May 5	5.31	5,850	56	30	10	2

Examination of Feces

Date	
May 1	Gray, no bile present
May 6	Clay-colored

Chemical Examination of Blood

Date	Icterus index	Van den Bergh reaction	Total (gm. %)	Serum protein Albumin (gm. %)	Globulin (gm. %)	A/G ratio
May 2	164	+				
May 3	132	+				
May 5	120	+				
May 25	120		5.4	1.5	3.9	0.45

Case 27

Clinical Course. The patient was a white male, 33 years of age. On May 13, he complained of headache, nausea and malaise. May 20: "dark" urine. May 23: light-colored stools; moderate degree of jaundice. Upon admission on May 23, did not appear acutely ill; liver moderately tender. May 26: no complaints. May 29: appetite decreased, jaundice more marked. Condition remained the same until June 3, when liver became moderately enlarged, tender. June 5: considerable epigastric distress. June 9: became delirious and irrational, slight convulsive movements; blood pressure, 116/64; temperature, pulse and respiration normal. June 11: after return to normal mental state, again extremely restless and semi-delirious; spasmodic movements at intervals, such as jerking of head and contracting of abdominal muscles, not convulsive; at times answered questions rationally, at other times was irrational; intensely jaundiced; no vomiting; later in day became very drowsy, fell asleep while examined. June 12: delirium persisted, noisy, very restless; cried out as if in pain; later comatose. June 13: condition essentially unchanged. June 14: much improved; responded to questions and was rational for short periods. June 15: again delirious; positive Babinski reflex; ankle clonus. June 16: vomited coffee-ground material; later, deep coma. June 17: bronchopneumonia evident; condition very poor. May 23 to June 11: temperature, 97.6° to 98.4° F.; pulse, 68 to 80; respiration, 18 to 20. June 11 to June 17: slightly febrile, temperature was 99.2° to 100.0° F. June 17: died.

Laboratory Findings.

Date	Icterus index	Chemical Examination of Blood				
		Nonprotein nitrogen (mg. %)	Sugar (mg. %)	Total (gm. %)	Albumin (gm. %)	Globulin (gm. %)
May 26	42					
June 11	200	40	62			
June 12		44	70	6.2	3.0	3.2
June 15		45	112			
June 16	160					

Date	Blood Counts			
	Red blood cells (millions)	White blood cells	Polymorphonuclear leukocytes (per cent)	Lymphocytes (per cent)
June 12	4.8	10,000	81	16
June 16	4.5	10,000		

Date	Urinalyses	
	Albumin	Bile
June 12	+	+
June 15	+	+
June 16	+	+

Case 76

Clinical Course. The patient was a white female civilian, 27 years old. She had not received yellow fever vaccine. In April, her husband, an officer, had a mild attack of hepatitis which lasted about 1 month. The patient herself was well until August 1, 1942, when general malaise developed and her appetite began to fail. August 25: jaundice developed. Admitted on September 5, moderately jaundiced; blood pressure, 118/78; liver tender and moderately enlarged. During her early stay in the hospital was occasionally jaundiced but felt fairly well; appetite was good. September 9: jaundice had deepened; definite nausea. Uneventful, afebrile course with small improvement until October 11, when swelling of face developed due to infection of right lower molar tooth; slight irregular fever during this period; jaundice was decreasing. October 15: diplopia developed and continued. October

28: speech became like that of an intoxicated person; normal clear-cut pronunciation altered so that her words were difficult to understand. October 30: very emotional, alternating periods of euphoria and crying; disoriented with regard to time, but oriented with regard to place and person; speech thick and slurred; deep and superficial reflexes normal, no abnormal reflexes could be demonstrated; general decrease in motor power and muscle tone which was attributed to poor physical condition rather than to involvement of central nervous system; clinical impression of acute toxic encephalitis. October 31: violently delirious, screamed and tried to get out of bed; unable to take food by mouth. November 2: twitching movements of hands and feet. There had been a gradual rise in temperature to 106° F. from October 30 to November 4. November 4: died.

Laboratory Findings.

Date	Blood Counts			
	Red blood cells (millions)	White blood cells	Polymorphonuclear leukocytes (per cent)	Lymphocytes (per cent)
Sept. 5	3.4	4,300	65	30
Oct. 20	2.7	4,400	69	31
Oct. 22	2.7	4,700	70	27
Nov. 2	2.8	11,600	89	7

Chemical Examination of Blood						
Date	Icterus index	Urea nitrogen (mg. %)	Nonprotein nitrogen (mg. %)	Total (gm. %)	Serum protein Albumin (gm. %)	Globulin (gm. %)
Sept. 7	100					
Sept. 9	109					
Sept. 14	123					
Sept. 25	154					
Oct. 5	147					
Oct. 12	156					
Oct. 29	76					
Nov. 3	116	34	64	7.2	3.9	3.3

Urinalyses

During early stay in hospital, no albumin; later, trace to moderate amount.

Case 121

Clinical Course. The patient was a white female civilian, 23 years of age, who had not received yellow fever vaccine. About December 1, 1942, there was dyspepsia, constipation, lassitude, progressive weakness; suddenly became jaundiced. December 18: admitted. December 19: temperature, 98° F.; pulse, 80; respiration, 18; blood pressure, 110/70; albuminuria; jaundice cleared considerably. By January 22, icterus index had fallen to 148. General condition improved; patient returned to her home. Upon readmittance on January 28, abdomen was distended; moderate irregular fever; complained of general aching. February 6: paracentesis, 1600 cc. of bile-stained fluid removed. February 8: fluid formed rapidly; patient became stuporous and irrational, later comatose; general condition poor. February 10: died.

Laboratory Findings.

Date	Blood Counts	
	Red blood cells (millions)	White blood cells
Dec. 19	4.8	8,400
Feb. 3	3.6	5,100
Feb. 6		8,100

Date	Icterus index	Chemical Examination of Blood	
		Urea nitrogen (mg. %)	Sugar (mg. %)
Dec. 19	188		
Jan. 22	148		
Feb. 6	140		
Feb. 7		22	104
Feb. 9	186		

Ascites. Ascites was common, occurring in about two-thirds of the cases. In many cases the day of appearance of ascites was known. The records stated that on one day the patient's abdomen was flat, and on the next it became distended. Thus, the onset of ascites was usually sudden. Ascites was a late manifestation; usually occurring only a few days before death (Table VII). There was one instance in which marked ascites developed relatively early, and after lasting several days disappeared.

TABLE VII
Interval Between Onset of Ascites and Death in 45 Cases of Epidemic Hepatitis

Interval (days)	No. of cases	Per cent of cases
1-4	22	49
5-9	10	22
10-14	3	7
15-19	4	9
20 and over	6	13

Case 100

Clinical Course. The patient was a white male, 27 years old. On June 12, appetite was poor; nausea but no vomiting; urine "dark"; itching at night. Some days later became severely nauseated but did not vomit; stools clay-colored; noticed that fatty foods particularly disagreed with him; slight pain in right upper quadrant. Admitted on June 22, with moderate jaundice; blood pressure, 130/60; abdomen flat; liver slightly tender, not enlarged. Condition remained about the same until June 28; patient was eating well; had no complaints; was ambulatory. July 4: jaundice deepened; still afebrile; went to mess hall and ate well. July 12: condition remained as stated. July 15: complained of not feeling well; jaundice of about same intensity; liver now painful and tender, not enlarged; no fever. July 20: had been vomiting; liver moderately enlarged; complained of pain in right upper quadrant; no abdominal fluid; no edema. July 21: nauseated; uncomfortable; pain in epigastrium; vomited occasionally; looked sick. July 22: abdominal fluid suspected; liver markedly tender; much pain in right upper quadrant; slight fever; seemed much worse; flanks slightly bulging. July 23: temperature, pulse and respiration were normal; abdomen more distended. July 24: slight rise in temperature; blood pressure, 120/65; abdominal fluid; suggestion of edema around ankles. July 25: paracentesis, 3500 cc. of bile-stained fluid removed; temperature, 101° F.; stools contained bile. July 26: condition considerably better; edema of ankles had cleared, but abdominal fluid had again accumulated. July 27: paracentesis, 3300 cc. of fluid withdrawn. July 28: continued to run low-grade fever; abdominal fluid recurrent; patient remained conscious and rational; liver slightly enlarged, but not tender. July 29: paracentesis, 2700 cc. of fluid withdrawn; liver still palpable, not

tender. July 30: patient in good spirits; felt better; temperature, pulse and respiration were normal; "ate three times today and for lunch had a lean steak." August 3: felt better, more alert, but had low-grade fever. August 5: paracentesis, 2300 cc. of fluid withdrawn. August 8: abdomen flat; no fluid; liver at costal margin; appetite still good. August 16: patient was not interested in food or in his surroundings; low-grade fever (temperature, 99.0° to 99.6° F.). August 21: no interest whatever; reflexes hypertonic. August 25: speech slurred and indistinct; response slow and frequently unintelligible; temperature, 100° F.; liver apparently had shrunk. August 28: bilateral ankle clonus, bilateral Babinski reflex; superficial reflexes hyperactive. August 31: stuporous. September 5: comatose; made smacking noises with lips; convulsive jerks of eyeballs; temperature, pulse and respiration were essentially normal. September 10: gradual rise in temperature to 104° F. on day of death. September 13: died.

Laboratory Findings.

Date	Specific gravity	Urinalyses		
		Albumin	Sugar	Bile
June 23	1020	o	None	+
July 21	1015	o	None	+
July 25	1013	o	None	
July 27	1015			
Aug. 19	1014	+	None	
Aug. 31	1004	++++	Trace	
Sept. 8	1028	Trace	++	
Sept. 11	1014	++++	+	
Sept. 13	1020	+++	+	

Chemical Examination of Blood

Date	Icterus index	Nonprotein nitrogen (mg. %)	Serum protein		
			Total (gm. %)	Albumin (gm. %)	Globulin (gm. %)
June 23	90				
July 21			5.28	2.79	2.49
July 23	116	43.5			
July 26	135	35			
July 30	92				
Aug. 7	50	35			
Aug. 17	57	36	8.24	6.68	1.56
Aug. 24	37				
Sept. 4	28				

Symptoms and Laboratory Findings

Analysis of symptoms and the results of laboratory examinations have been restricted to the following: temperature, pulse rate, blood pressure, examination of liver by palpation, recurrence of attack, hemorrhages, red blood count, leukocyte count, differential white count, plasma proteins and icterus index. In this analysis, the intermediate phase has arbitrarily been divided into two periods, namely, the first 3 days after the onset of jaundice, and the later period.

Temperature. An analysis of temperature is given in Table VIII. It will be seen that 92 per cent of the patients were afebrile during the first 3 days after the onset of jaundice. However, subsequent to this period 41 per cent developed fever. This usually was of brief duration. Since in many cases plasma, glucose, or whole blood was administered

intravenously, the febrile episodes cannot, with certainty, be attributed to hepatitis. Perhaps the most significant fact of the analysis is that approximately 60 per cent of the patients were afebrile throughout the intermediate period, but during the final period fever developed in the great majority, 89 per cent. Usually there was a sharp rise in temperature during the last 2 or 3 days of life when the patient was moribund (Text-Fig. 3).

Pulse Rate. In contrast to the bradycardia which is so common in other hepatic diseases, slowing of the pulse in this series was observed but seldom.

TABLE VIII
Temperature in Cases of Epidemic Hepatitis

	Number of cases		
	Intermediate period		Final period
	First 3 days after jaundice	Subsequent to first 3 days after jaundice	
Afebrile	24 (92%)	20 (59%)	6 (11%)
Febrile	2 (8%)	14 (41%)	49 (89%)
Total no. of cases	26	34	55

Blood Pressure. During the intermediate period the blood pressure was usually normal. With the onset of nervous manifestations, the pressure tended to rise. Representative examples follow: 144 systolic, 94 diastolic; 170/90; 100/80; 155/70; 150/92.

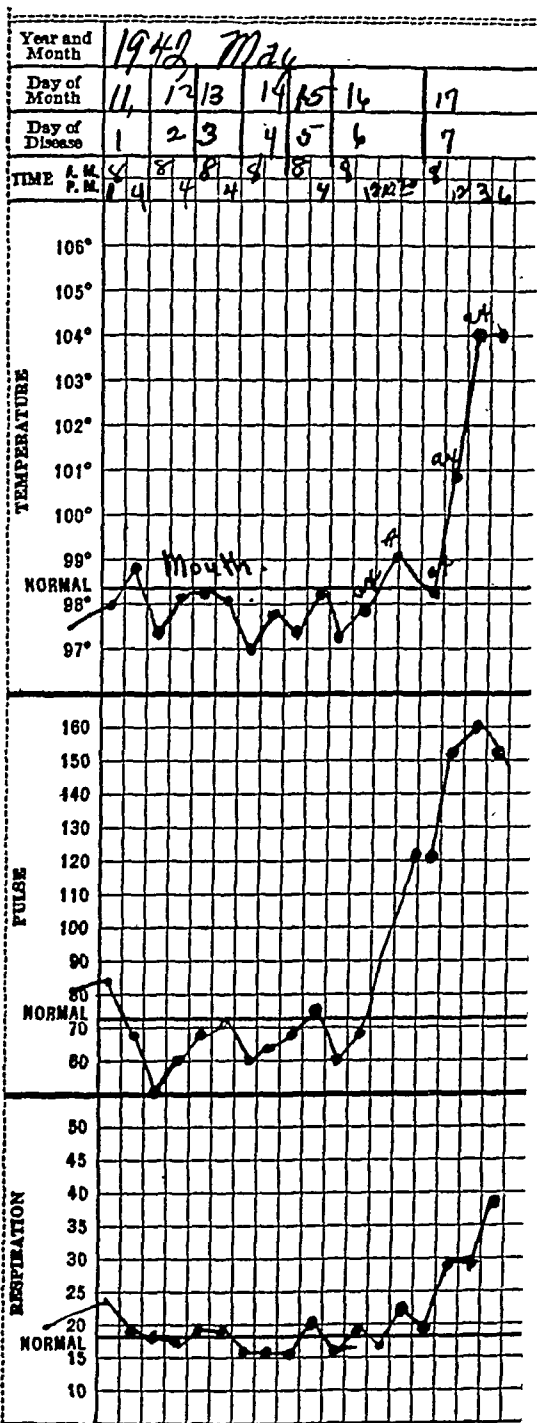
Palpation of Liver. During the first 3 days after the onset of jaundice, enlargement of the liver was found in approximately one-half the patients (15 of 28). Later, in the intermediate stage, enlargement was still more common (29 of 34 cases). Enlargement was usually associated with tenderness. During the final phase the majority showed shrinkage of the liver.

Recurrence. In only one instance did symptoms recur after an apparent recovery.

Case 117

Clinical Course. The patient was a white male, 22 years of age. In April, 1942, he noticed increased malaise and frequent nosebleeds. He later became jaundiced and was admitted to hospital, where he remained for 7 weeks. Course was uneventful except for daily rise in temperature, which usually reached a peak of 103° F. in the evening. Icterus index was as high as 113. His course, except for the fever, was similar to that of about 20 other patients with jaundice who were at that time hospitalized. June 8: transferred to another hospital; moderately ill, undernourished and jaundiced; liver enlarged and tender. Icterus index varied from 20 on admission to 120 on July 27, and then gradually fell to 11. Afebrile. Temperature, pulse and respiration had been normal since June 23. Steady improvement in general condition. September 14 to October 13: sick leave. October 27:

returned to duty. November 27: again became jaundiced. December 5: readmitted, apparently not acutely ill. December 11: ambulatory; did not feel ill, no fever. December 14: nausea and vomiting; jaundice had deepened; dull aching pain in right upper quadrant; stools had varied from clay-colored to light gray. December



Text-Figure 3

18: icterus index, 110; white blood cells, 4,500. December 20: icterus index, 150. December 21: vomited bile-stained material; stools brown. December 23: jaundice somewhat decreased; slight soreness in right upper quadrant. December 28: definitely worse; disoriented; later semicomatose and stuporous. December 29: died.

Hemorrhages. Hemorrhages were common, especially in the late period. Their incidence and distribution were as follows: petechiae of the skin in 20 instances, vomiting of blood in 20, epistaxis in 11 and other hemorrhagic phenomena (bleeding from bowel, hematuria and bleeding from respiratory tract) in 16 instances.

Blood Counts and Hemoglobin Determination. Representative examples of blood counts and hemoglobin determinations from 7 cases are given in Table IX. The differential white counts include only neutrophils and lymphocytes.

Erythrocyte Count. Erythrocyte counts in the different phases of hepatitis are summarized in Table X. During the first 3 days after

TABLE IX
Blood Counts in Representative Cases

Case no. and duration	Date	Red count	Hemo-globin	White count	Neutrophils	Lymphocytes
		(million)	(per cent)		(per cent)	(per cent)
No. 25. A.M.M.* no. 83171						
Onset, 5/29/42	6/6/42	4.26	75	7,500	64	32
Death, 6/27/42	6/26/42	3.88	70	4,550	57	34
No. 30. A.M.M. no. 83312						
Onset, 5/24/42	5/28/42	4.41	85	6,800	52	48
Death, 6/18/42	6/19/42	4.00	80	5,200		
No. 52. A.M.M. no. 83747						
Onset, 4/30/42	5/14/42	4.50	80	4,250		
Death, 9/15/42	7/8/42	3.10	80	13,500		
	7/15/42	3.80	80	9,100		
	8/2/42	2.75	55	10,800		
No. 59. A.M.M. no. 83833						
Onset, 6/4/42	7/7/42	4.65	78	8,000	50	41
Death, 7/13/42	7/8/42	4.55	75	7,000	65	30
	7/13/42	3.73		5,000	79	21
No. 84. A.M.M. no. 84422						
Onset, 5/24/42	6/16/42	4.6	80	3,600	51	49
Death, 8/27/42	6/21/42	5.3	95	9,200	56	44
	6/23/42			2,800	40	60
	7/2/42			5,600	50	50
	7/6/42	4.9	80	4,100	64	36
	7/29/42	4.3	85	4,400	63	37
	8/12/42	3.2	75	5,300	78	21
	8/14/42					
	8/18/42	2.9		4,900	68	30
	8/24/42	4.0	80	9,400	84	15
No. 86. A.M.M. no. 84506						
Onset, 5/25/42	6/21/42	4.50		6,700		
Death, 7/26/42	7/7/42	3.25	80	4,200	67	33
	7/16/42	3.00	75	5,800		
	7/19/42	2.20	65	5,600	63	37
	7/25/42	3.47	65	9,700		
No. 100. A.M.M. no. 85431						
Onset, 6/12/42	6/22/42	4.1	85	6,400	70	29
Death, 9/13/42	7/20/42			6,200	63	33
	7/23/42	3.8	87	5,500	62	38
	8/2/42	3.9		7,700	61	38
	8/11/42	3.2		9,000	65	32
	8/12/42			7,100	75	35
	8/16/42	4.3		9,500		
	8/24/42	3.1	73	7,700	74	21
	9/10/42			21,000	80	20
	9/10/42		76	22,000	83	17
	9/11/42	3.7		31,000	83	18

* A.M.M. = Army Medical Museum.

jaundice developed, the counts were approximately normal. Later the erythrocyte count fell. During the final phase definite anemia of secondary type was evident in approximately 40 per cent of the cases.

Leukocyte Count. The results of leukocyte counts are given in Table XI. Slight leukopenia was evident in nearly half of the cases early in

TABLE X
Erythrocyte Count in Cases of Epidemic Hepatitis

Erythrocyte count	Number of cases		
	Intermediate period		Final period
	During first 3 days after jaundice	Subsequent to first 3 days after jaundice	
(millions)			
Over 5	5 (22%)	9 (27%)	9 (24%)
4—4.9	18 (78%)	16 (48%)	14 (38%)
3—3.9	0	5 (15%)	10 (27%)
2—2.9	0	3 (9%)	4 (12%)
Total number of cases	23	33	37

the intermediate phase. Leukocytosis during the intermediate period occurred in relatively few. The counts during the final period were strikingly different. Then few patients showed leukopenia, the majority having mild leukocytosis. This leukocytosis was probably related to terminal events, such as lobular pneumonia and phlegmonous inflammation of the gastrointestinal tract.

Differential White Blood Cell Counts. The results of differential

TABLE XI
Leukocyte Count in Cases of Epidemic Hepatitis

Leukocyte count	Number of cases		
	Intermediate period		Final period
	During first 3 days after jaundice	Subsequent to first 3 days after jaundice	
(thousands)			
Below 3.0	0	1 (2%)	1 (2%)
3.0—3.9	0	0	1 (2%)
4.0—4.9	5 (17%)	4 (10%)	4 (7%)
5.0—5.9	9 (30%)	9 (22%)	1 (2%)
6.0—6.9	2 (7%)	7 (17%)	5 (9%)
7.0—7.9	3 (10%)	9 (22%)	4 (7%)
8.0—8.9	6 (20%)	6 (15%)	6 (11%)
9.0—9.9	3 (10%)	1 (2%)	6 (11%)
10.0—10.9	1 (3%)	2 (5%)	7 (13%)
11.0—11.9	0	0	0
12.0—12.9	0	0	7 (13%)
13.0—13.9	1 (3%)	0	2 (4%)
14.0—14.9	0	1 (2%)	7 (13%)
15.0 and over	0	1 (2%)	5 (9%)
Total number of cases	30	41	56

counts are shown in Table XII. In this table the dotted horizontal lines mark the boundary between the normal and the abnormal. There was a relative lymphocytosis in two-thirds of the cases during the early days of the intermediate period. By contrast, during the final period a relative lymphocytosis was uncommon.

Plasma Proteins. In severe damage to the liver the plasma proteins would be expected to fall. In this series such a fall frequently did not

TABLE XII
Differential White Blood Cell Counts in Cases of Epidemic Hepatitis

	Number of cases		
	Intermediate period		Final period
	During first 3 days after jaundice	Subsequent to first 3 days after jaundice	
Polymorphonuclear leukocytes (per cent)			
40—49	0	2 (10%)	0
50—59	5 (28%)	6 (30%)	3 (12%)
60—69	10 (56%)	10 (50%)	2 (8%)
70—79	3 (17%)	2 (10%)	10 (38%)
80—89	0	0	8 (31%)
90 and over	0	0	3 (12%)
Total number of cases	18	20	26
Lymphocytes (per cent)			
50—59	0	2 (10%)	0
40—49	5 (28%)	7 (35%)	1 (4%)
30—39	7 (39%)	2 (10%)	4 (15%)
20—29	5 (28%)	8 (40%)	9 (35%)
Below 20	1 (6%)	1 (5%)	12 (46%)
Total number of cases	18	20	26

occur, probably because of therapeutic administration of plasma or whole blood. Representative examples are given in Table XIII.

Icterus Index. The icterus index in a number of representative cases, together with clinical abstracts, is given in Table XIV. The index is above normal. It fluctuates irregularly, but in the majority of cases it tends to rise. Exceptions to this are summarized in Table XV.

The icterus index during the three phases of hepatitis is shown in Table XVI. During the first 3 days the index was below 100 in the great majority of the cases. Subsequently it tended to rise, particularly so in the final period.

PATHOLOGIC ANATOMY

As has been stated, in every instance the fatal cases of epidemic hepatitis presented lesions in the liver that correspond to so-called idiopathic yellow or red atrophy. This condition has been described

in detail by numerous writers, and the literature on the subject has been exhaustively summarized by Roman⁴³ and by Herxheimer and Thölldte.⁴⁴ The paper by Wilson and Goodpasture⁴⁵ serves as an excellent introduction to the subject. It would be repetitious, therefore, to go into morphologic minutiae.

The changes observed will be presented in the following order: liver,

TABLE XIII
Plasma Proteins in Representative Cases
(gm. per 100 cc.)

Case no. and duration	Date	Total protein	Albumin	Globulin	Remarks
No. 52. A.M.M.* no. 83747 Onset, 4/30/42 Death, 9/15/42	5/16/42	6.5	3.7	2.8	No ascites
	5/29/42	6.9	5.2	1.6	
	6/ 6/42	7.7	3.0	3.9	
	6/15/42	6.7	4.4	3.3	
	6/29/42	5.5	3.1	2.9	
	7/15/42	5.0			
	7/20/42	5.4			
	7/29/42	6.7			
	8/ 5/42	7.2	4.9	2.3	
	8/10/42	7.6	5.0	2.6	
	8/17/42	7.3	5.7	1.5	
	8/24/42	9.2	6.5	2.4	
	8/31/42	7.2	4.7	2.5	
	9/ 7/42	7.2			
No. 84. A.M.M. no. 84422 Onset, 5/24/42 Death, 8/28/42	7/ 8/42	5.26	3.31	1.95	Ascites since 7/2/42; repeated paracente- ses
	7/13/42	4.40	2.75	1.65	
	7/16/42	4.9			
	7/20/42	4.69	2.87	0.15	
	7/23/42	3.61	2.10	1.27	
	7/29/42	3.99	2.59	1.14	
	7/30/42	5.14	2.54	2.40	
	8/ 3/42	5.08	3.03	2.05	
	8/13/42	5.90	3.65	2.25	
No. 89. A.M.M. no. 84856 Onset, 6/1/42 Death, 8/18/42	6/25/42	5.68			Ascites dur- ing last few days of life
	7/ 4/42	6.6	4.3	2.3	
	7/20/42	6.65	3.7	2.6	
	8/10/42	4.1			
	8/15/42	3.4			

* A.M.M.=Army Medical Museum.

gallbladder, regional lymph nodes, ascites, spleen, gastrointestinal tract, hemorrhagic phenomena, bone marrow, kidney, testis, and brain.* No significant changes were found in the other organs.

Since no verbal description can give an adequate picture of the gross and microscopic changes of any disease, this paper is liberally documented by photographic illustrations.

* Major Philip Custer examined many sections of the bone marrow and spleen, and Captain Webb Haymaker those of the brain. This study has been greatly aided by their advice.

Liver

In all cases the liver is the site of the principal lesions and presents a characteristic picture. Without exception the changes are typical of idiopathic yellow atrophy.

Gross Appearance of the Liver

Grossly the organ is usually reduced, at times to less than one-half its normal size. Most often it weighs between 800 and 1200 gm. Reduction in weight, however, is not invariably found; in approximately one-fifth of the cases the weight of the liver falls within normal limits or is actually above the normal. Generally speaking, the smallest livers

TABLE XIV
Icterus Index in Representative Cases

Case no. and duration	Date	Icterus index	Clinical abstract
59 Onset, 6/4/42 Death, 7/13/42	6/13	36	White, male, 26 years old. 6/4: weakness, nausea, headache, anorexia, generalized aching, "dark" urine. 6/12: admitted; temperature, pulse and respiration normal; blood pressure, 114/80. 6/15: liver slightly enlarged. No change until 6/26, then abdominal pain; liver more enlarged and tender. 6/29: stuporous; occasional nausea and vomiting; apathetic. 7/3: jaundice increased. 7/8: blood pressure, 146/80; liver at costal edge. 7/10: blood pressure, 140/90; seemed less toxic; ate breakfast; responded to questions. 7/12: abdomen distended. 7/13: temperature, pulse and respiration began to rise; ascites noted; blood pressure, 140/78; temperature, 102° F. in morning, rose to 104° F. by afternoon; pulse, 130 to 150; respirations, 30 to 40.
	6/17	78	
	6/24	143	
	6/29	127	
	7/1	136	
	7/7	177	
	7/10	210	
	7/11	190	
	7/13	204	
57 Onset, 5/26/42 Death, 7/9/42	6/8	28	White, male, 20 years old. About 5/26: weakness, anorexia, nausea, headache, "dark" urine; later jaundice; said to have lost about 10 pounds; no itching. 6/8: admitted; ambulatory; not acutely ill; blood pressure, 104/68. Course in hospital stormy; persistent nausea and vomiting; deepening jaundice. 6/10: marked increase in size of liver to 4 fingersbreadth below costal margin; thereafter gradual decrease, by 6/30 to costal rim, during last week of life to 3 fingersbreadth above costal rim. 7/3: stuporous; comatose; spasmodic twitching of facial muscles; blood pressure, 84/50.
	6/15	30	
	6/18	32	
	6/22	30	
	6/26	40	
	6/29	50	
84 Onset, 5/24/42 Death, 8/28/42	6/20	160	White, male, 24 years old. About 5/24: anorexia, headache, backache, "dark" urine, clay-colored stools. 6/1: sclerae icteric. 6/4: admitted. Until 6/16, felt fairly well; then malaise, nausea, vomiting; liver tender, enlarged; "prognosis appears to be good." 7/2: ascites; repeated paracenteses. 7/23: jaundice declining; general condition improved. 8/10: appetite good. 8/13: greatly improved; condition satisfactory. 8/15: condition changed; became restless; dull; drowsy. 8/16: symptoms more marked; speech scanning; disoriented; progressive decline. During last several days ran irregular fever, temperature of 103° to 104° F.
	6/29	160	
	7/6	150	
	7/8	150	
	7/10	150	
	7/18	100	
	7/20	90	
	7/24	60	
	7/27	60	
	7/30	45	
	8/7	45	
	8/10	35	

TABLE XIV (Continued)
Icterus Index in Representative Cases

Case no. and duration	Date	Icterus index	Clinical abstract
23 Onset, 4/29/42 Death, 5/27/42	5/5 5/9 5/11 5/13 5/21 5/23 5/25	28 80 180 170 224 146 106	White, male, 26 years old. 4/29: nausea, vomiting, headache, constipation. 5/3: sclerae yellow. 5/5: admitted; temperature, pulse and respiration normal; liver not enlarged, slightly tender; blood pressure, 96/60; stools clay-colored. Remained in approximately same condition until 5/22, when jaundice became marked and vomiting began; liver markedly tender. 5/26: very restless; vomiting. 5/27: vomiting dark material containing blood; comatose.
52 Onset, 4/30/42 Death, 9/15/42	5/16 6/5 6/15 6/18 6/29 7/6 7/15 7/20 7/27 7/29 8/3 8/10 8/17 8/24 8/31 9/7	170 285 200 300 290 261 200 167 176 235 182 210 236 201 300 322	White, male, 27 years old. 4/30: nausea and anorexia. 5/2: "dark" urine. 5/4: jaundice; itching. 5/11: admitted; afebrile; liver just palpable. 6/17: said to have lost 21 pounds in 4 weeks; at times dull aching pains over region of gallbladder; thought to be due to obstruction of ducts. 6/22: exploratory operation; liver slightly enlarged, no gross abnormality; specimen taken for biopsy; gallbladder was small, wrinkled, almost empty, no stones; common duct was small, no stones. 7/15: edema of feet and ankles; marked itching. 8/3: itching continued; strength good. 8/10: patient continued to be up and about; felt well except for itching. 8/18: condition the same. 8/25: slightly weaker; irritable; appetite was less. 9/1: was gradually becoming weaker, walking only with crutches. 9/6: very weak, confined to bed; irrational at times. 9/14: comatose; weak; appeared to be dying from sheer exhaustion.

occur in patients who have died within 5 weeks. At later periods, weight loss tends to be replaced by compensatory hyperplasia of the remaining parenchyma.

The surface is usually smooth or finely wrinkled in the early case; at this stage its color is variable and not distinctive. Later, ivory colored or yellowish green coarse nodules, or larger, tumor-like masses project from the surface of the organ in some regions, whereas elsewhere the surface is sunken, dull red or grayish. The consistency, also, is variable. Usually flaccid in the early stages, the collapsed parts soon be-

TABLE XV
Trend of Icterus Index in 51 Cases of Epidemic Hepatitis

Trend	No. of cases	Per cent of cases
Remains below 50	6	12
Rises steadily	33	65
Rises, falls:		
(A) Rises, then falls slightly	9	22
(B) Rises, then falls to nearly normal	2	
Rises, then falls and afterwards rises again	1	2

come tough and meat-like. The nodular parts differ but little from the consistency of normal liver.

On the *cut surface* the irregular distribution of the lesions is even more conspicuous. There are large, red, meat-like areas which ooze blood, and in which the landmarks are indistinct or obliterated. In sharp contrast to these red areas are irregularly distributed patches of pale yellow or bile-tinted tissue which are distinctly lobulated. These yellow patches range in size from small nodules to large confluent masses which may occupy the major part of the organ. The component

TABLE XVI
Icterus Index in Cases of Epidemic Hepatitis

Icterus index	Number of cases		
	Intermediate period		Final period
	During first 3 days after jaundice	Subsequent to first 3 days after jaundice	
Below 50	8 (35%)	2 (3%)	4 (8%)
50-99	12 (52%)	12 (20%)	7 (13%)
100-149	2 (9%)	18 (30%)	6 (11%)
150-199	1 (4%)	16 (27%)	9 (17%)
200-249	0	7 (12%)	10 (19%)
250-299	0	2 (3%)	9 (17%)
300-349	0	1 (2%)	5 (10%)
350-399	0	1 (2%)	2 (4%)
400 and over	0	1 (2%)	1 (3%)
Total	23	60	53

lobules are abnormally large and vary greatly in size and shape. This tissue is ischemic. Usually it has a "healthy" appearance; it is not fatty nor turbid.

The relation of size of the liver to duration of the disease is given in a graph (Text-Fig. 4), and the data from which the graph was constructed are presented in Table XVII. Disregarding for the present the association with ascites, it will be seen that marked reduction in size generally occurs when the duration of the disease is short, whereas large livers are more often found when the course has been protracted.

Irrespective of the duration of the disease, the weights of the liver show considerable scattering; they range from 600 to 2400 gm. In approximately one-fifth of the cases, the weight of the liver is normal or above normal (taking 1400 to 1600 gm. as the average normal weight). In four-fifths of the cases the liver is smaller than normal. This reduction is extreme in 10 livers, which weigh from 600 to 800 gm. Hence, the liver in yellow atrophy usually is shrunken, but occasionally is enlarged.

The variability in size is equalled by the variability in shape, color, consistency and appearance of the cut surface. This variability is

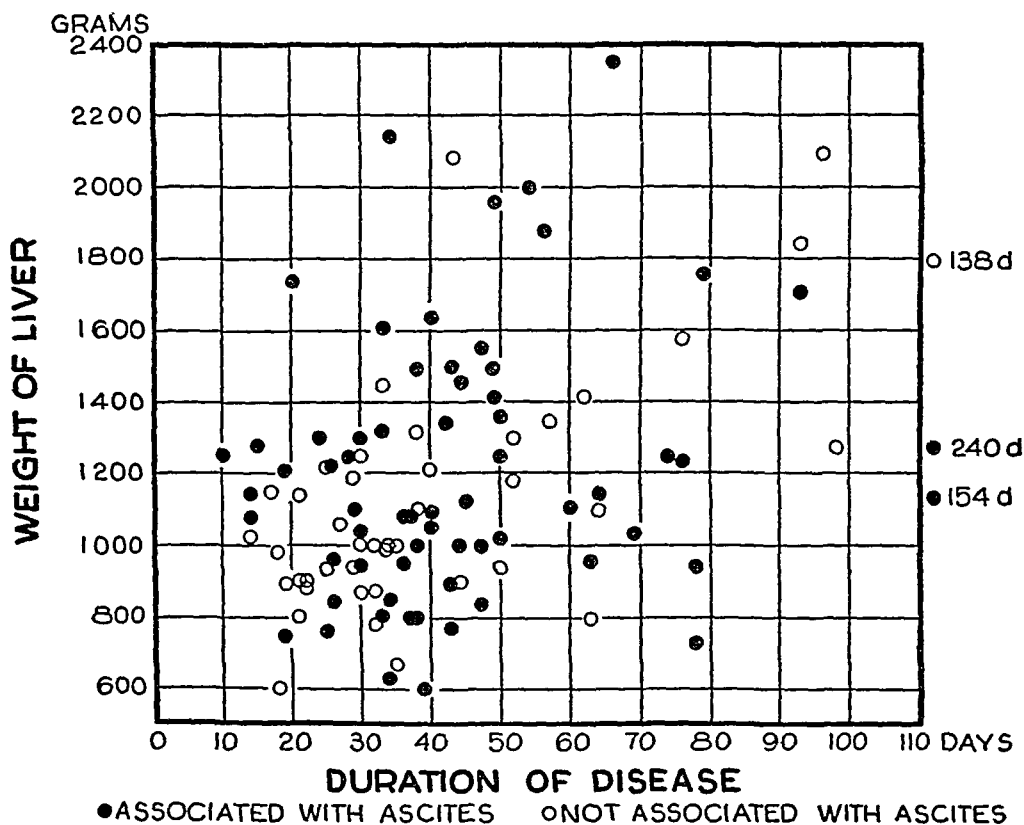
TABLE XVII
Relation of Duration of Disease to Size of Liver and Occurrence of Ascites in 108 Cases of Epidemic Hepatitis

Duration of disease	Weight of liver (gm.)														Total		Grand total
	600-799		800-999		1000-1199		1200-1399		1400-1599		1600 and over						
	Ascites	No ascites	Ascites	No ascites	Ascites	No ascites	Ascites	No ascites	Ascites	No ascites	Ascites	No ascites	Ascites	No ascites			
(days) 10-19	1	1		2	2	2	3	0					6	5	11		
20-29	1		2	6	1	3	3	1			1		8	10	18		
30-39	2	2	6	2	4	6	2	2	1	1	2		17	13	30		
40-49	1		2	1	5		1	1	5		2	1	16	3	19		
50-59				1	1	1	1	2			3		5	4	9		
60 and over	2		1	1	4	1	2	1		2	4	3	13	8	21		
Total	7	3	11	13	17	13	12	7	6	3	12	4	65	43	108		
Grand total	10		24		30		19		9		16		108				

characteristic of epidemic hepatitis; the liver is not damaged uniformly, but the extent of damage in different areas varies widely. Large masses of parenchyma are destroyed completely, whereas elsewhere damage is moderate.

The gross changes found may now be briefly described in representative cases.

The External Appearance of the Liver. The liver shown in Figure 1 represents the external appearance seen in the majority of cases. The



Text-Figure 4

duration of hepatitis was 36 days. The liver weighed 1320 gm. The left lobe is seen to be disproportionately shrunken. The surface is uneven and varies in color. Over approximately half of the right lobe, the tissue protrudes in the form of irregularly elevated, yellow nodules. Elsewhere, the surface is sunken, gray-red, and the capsule is smooth or finely wrinkled. In the left lobe the surface is deeply furrowed. When fresh the consistency of this lobe was meat-like; by contrast, the yellowish elevations of the right lobe felt approximately like normal liver.

A much greater shrinkage and deformity of the liver is shown in Figure 10, although in this case the duration of hepatitis was prac-

tically the same as in the case from which the preceding one was obtained, namely, 37 days. The organ weighed 800 gm. Large, yellowish green bosses project from the surface. Between these, the surface is grayish red, smooth, or finely wrinkled. Thus, in two cases of practically the same duration, the livers appear very different.

An even greater deviation is shown in Figure 9. The duration of hepatitis was 69 days. The liver weighed 1040 gm. Many large, greenish masses project like tumors above sunken, reddish patches, the surface of which has the appearance of coarsely grained leather. In gross appearance this liver is reminiscent of *hepar lobatum*.

The *cut surface* of the liver in one of the early cases of the series is shown in Figure 2. The duration of hepatitis was 19 days, and the weight of the liver was 890 gm. In the right lobe are large confluent nodular areas of ivory color. They are notably ischemic. Lobulation is distinct; most of the individual lobules are conspicuously large. In contrast to the ischemic yellow areas the cut surface of the rest of the liver is uniformly reddish brown. Because of the color, there is a superficial resemblance to liver parenchyma, but there is no lobular pattern.

Little further change in the appearance of the cut surface is shown at a later stage of hepatitis, 43 days in duration (Fig. 3). The organ weighed 850 gm. Two contrasting regions are seen, one a yellow-green nodular mass, the other, a reddish brown, meat-like tissue.

In the four examples given, the livers were shrunk. Enlarged livers are shown in Figures 11 and 12. Fig. 11 illustrates the cut surface of a liver which weighed 1710 gm. The duration of hepatitis was 93 days. Most of the tissue consists of strikingly large, pale lobules. They bulge above sunken, smooth tissue which, when fresh, was gray-red and firm.

Another enlarged liver (2100 gm.) is shown in Figure 12. The duration of the hepatitis was 96 days, *i.e.*, practically the same as in the preceding case. The entire right lobe is uniformly composed of irregular lobules having pale peripheries and dark centers. The left lobe is small and gray.

Microscopic Appearance

Parenchymal Destruction. In sections from the red areas, the liver cells have disappeared completely, but the lobules are still outlined by small proliferating bile ducts. The fact that, despite complete destruction of the parenchyma, the outlines of the lobules may still be recognized is highly characteristic of epidemic hepatitis. A low-power view of this appearance is shown in Figure 17. It is seen that, because of the disappearance of liver cells, the portal triads lie nearer together and that lobular outlines are indicated by small bile ducts. Greater

detail is shown in Figure 18, where numerous small bile ducts appear to form a fence around the lobules.

The *sinusoids* in areas of "red atrophy" are preserved and are often greatly engorged (Fig. 4). Sometimes, however, the sinusoids are collapsed, and grossly such areas appear gray.

The reticular *framework* of the lobules is not destroyed. Its meshes are narrowed, or even collapsed, and its fibers thickened. The preservation of the reticulum is shown in a case of average duration, 30 days, and in one of prolonged duration, 96 days (Figs. 19 and 20). Through this framework are scattered numerous lymphocytes, plasma cells, granulocytes and macrophages; their relative proportions vary from case to case, and with the duration of the disease. Thus, as the result of a destructive process, entire lobules throughout large areas of the liver are reduced to their skeletal frames. Here, an inflammatory reaction is evident; that is, a hepatitis.

Absence of Scarring in Areas of Destruction. Although the reticulum fibers may become densely compressed, there is little or no formation of collagen. Scarring such as occurs in cirrhosis and accompanies the healing of abscesses or gummas is characteristically absent in epidemic hepatitis.

Rapid Disappearance of Liver Cells. The sequence of events that have led to the emptying of the lobules cannot be traced with certainty. None of the livers in this series were in the early stages of destruction; indeed, so far as I have been able to learn from the literature, no one has ever seen the earliest stages in this disease, which rarely terminates in its most acute stages. All that is known with certainty is that cell destruction occurs rapidly and that cell debris is removed speedily. In the present series, by the tenth day (the earliest case of the series) practically all traces of dead cells have been swept away, presumably by enzymic action, and nothing remains in the lobules but vascular framework and inflammatory cells. We find here no evidence of slow cell death—fatty changes, coagulation of cytoplasm—such as are characteristically seen in yellow atrophies due to chemical poisons, bacterial toxins, yellow fever, or eclampsia. Rapidity and completeness of cell destruction is a distinguishing feature of epidemic hepatitis.

Distribution of Lesions in the Lobule. The destructive change usually, if not always, begins in the central part of the lobules, for in the earliest cases of the series only the central zones of the lobules are involved (Fig. 13). Even in more protracted cases many lobules are encountered in which the damage is limited to the central regions, leaving intact a peripheral rim of liver tissue (Fig. 14). The lesions do not involve all lobules to the same degree; they range from destruction of

approximately one-third of the central portions in the better preserved areas to complete destruction of all liver cells in large areas of the organ. Every conceivable intermediate step may be encountered. But whenever even a fragment of hepatic parenchyma remains, it is found in the peripheral zone. For example, in another early case, only scattered groups of liver cells are left at the lobular peripheries (Fig. 15).

Inflammatory Reaction. In epidemic hepatitis destruction of liver cells is invariably accompanied by an inflammatory reaction. By inspection of Figures 13 to 15, which show zones of destruction, it may be seen that the parts of the lobules from which the parenchyma has disappeared have a granular aspect. This granularity is due not to remaining débris but to the presence of inflammatory cells. In early stages polymorphonuclear leukocytes, lymphocytes, plasma cells and macrophages occur in approximately equal proportions (Fig. 16); later, the polymorphonuclear leukocytes become less numerous. The inflammatory cells linger in the depleted stroma for long periods, only gradually becoming less numerous. For example, in a case with a course of 240 days, the inflammatory changes did not differ appreciably from those in the average case of a few weeks' duration.

Lipofuscin. Conspicuous among the inflammatory cells are macrophages which have engulfed small granules of yellow-brown pigment (Fig. 6 a). This pigment is not dissolved in the process of preparing paraffin sections; in such sections it is stained by Sudan III and similar fat stains (Fig. 6 b). It is somewhat acid-fast, and can be demonstrated by the Ziehl-Neelsen method.

Silver stains, such as Wilder's reticulum stain, render the granules black. The pigment is lipofuscin, or so-called "waste-pigment."^{46, 47} Lipofuscin is probably a normal pigment of liver cells which is liberated and rapidly phagocytized when these cells disintegrate. It thus serves as an indicator of breakdown of hepatic parenchyma. Like the other types of cells previously discussed, the pigmented macrophages may persist for long periods.

Lipofuscin must be distinguished from another pigment that may also occur in the liver and which in recent years has attracted considerable attention, namely, ceroid. The main points of difference are that ceroid forms coarse globules that often lie extracellularly, it is strongly acid-fast and even less soluble in fat solvents than lipofuscin, and in paraffin it stains deeply with fat stains.⁴⁸

Endophlebitis of Efferent Blood Vessels. The efferent vessels show marked alterations. All but the largest hepatic veins are the site of endophlebitis. The process is seen particularly in the central lobular veins and in the sublobular veins (Figs. 21 and 22). In these vessels

the intima is densely infiltrated with cells of the same types as those scattered throughout the skeletal remnants of the lobules. Where inflammatory cells are abundant in the stroma, they are usually abundant in the intima of veins that drain the area. In early stages the endothelium of the intima is unbroken; in later stages it may become ruptured, spilling the invading cells into the vascular lumen. Rupture of the intima is commonly followed by thrombosis.

Not only the intima but other layers of the vessels are altered. Often their walls are greatly thickened, and have a hyaline appearance (Fig. 21). They usually stain rather lightly with eosin, but densely by the Masson-Mallory aniline-blue method for connective tissue. By silver impregnation methods, the walls of the veins are found to have a loose, fibrillar structure, which differs but little from the normal (Fig. 23). It is evident that the collagenous substance, which gives the hyaline appearance to the wall, lies between the component fibers, which themselves remain unchanged. Perhaps this collagenous substance becomes more prominent through imbibition of fluid.

Endophlebitis usually is more conspicuous in relatively early cases, although lesser degrees are found even in protracted cases. In the latter group, however, fibrous obliteration of the veins rather than acute inflammatory reaction is the more common.

This form of endophlebitis is not specific for the damaged liver of epidemic hepatitis. It may occur in other destructive processes involving liver parenchyma.

Hyperplasia of Liver Cells

The preceding sections have dealt with the microscopic appearance of the liver in areas which grossly are collapsed and red; here, the parenchyma has been destroyed. In contrast, in areas which appear nodular and yellow, the tissue is in a state of regenerative hyperplasia. An abundance of new parenchyma has formed by hypertrophy and multiplication of cells that have escaped destruction. The architectural pattern of the new parenchyma, however, only rarely approaches the normal; in most regions it is exceedingly atypical. The process of restoration begins early. By the tenth day numerous buds of binucleated or multinucleated liver cells extend from the remaining portions of the hepatic columns into the depleted stroma (Figs. 24 to 26). In less than 20 days a large mass of new liver tissue has formed. This tissue usually is composed of atypically built "lobules." They vary in size and shape. Most of them have fused with neighboring "lobules"; less often patches of parenchyma are isolated by bands of collapsed stroma.

The microscopic appearance of such a region in one of the earlier cases (19 days in duration) is illustrated in Figure 31. The section comes from the pale yellow part of the liver shown in a colored photograph (Fig. 2). Inspection of the photomicrograph discloses at once the absence of the lobular pattern characteristic of normal liver. Instead, the parenchyma consists of ill-defined patches, in none of which the component cords of cells converge toward a common central lobular vein. These patches represent hyperplastic remnants of former lobules.

An illustration of the atypical structural arrangement of the newly formed tissue in a case of prolonged duration (93 days) is given in Figure 32. There are seen great confluent patches of parenchyma but no typical lobules.

These two illustrations represent the microscopic picture observed in nearly every case. Only occasionally, and then in small areas only, is normal lobulation found restored (Fig. 33).

The hyperplastic parenchyma is composed chiefly of compact cords of liver cells, but often such cords have formed only at the periphery of the individual "lobules." The central part is frequently occupied by newly formed cells which are not organized into cords (Fig. 34).

Areas of regeneration are usually ischemic (Fig. 5). Well defined spaces, with endothelial lining, lie between the cell cords; but the blood content of the spaces is usually slight, and only in rare instances approaches the normal. The marked degree of ischemia of hyperplastic tissue stands in contrast to the great engorgement of the tissue in areas of "red atrophy" (Fig. 4).

The hyperplastic tissue differs from the normal not only in general arrangement but in structure of its component parts. The cords of liver cells are usually distinctly broader than the normal. In longitudinal sections the cords often have a conspicuous central cleft. In transverse sections the cords are seen to have a tubular structure; such tubules have from six to eight cells spaced around a lumen (Fig. 37). The clefts or lumina are dilated bile canaliculi. Many are obstructed with coarse branching masses of bile (Figs. 37 and 38). Throughout large areas, almost every canaliculus contains obstructing masses.

The individual liver cells generally are large. In some the cytoplasm is smooth; in others it contains coarse granules of bile. Fatty changes in the cells are rare. The nuclei are usually prominent, and the nucleoli are swollen and stain deeply (Fig. 36). Inclusion bodies, such as occur in many virus diseases, are not found.*

* I am grateful to Dr. Thomas Rivers of the Rockefeller Institute, to Dr. E. V. Cowdry of the Washington University School of Medicine, and to Dr. Alfred M. Lucas of Iowa State College for examining a number of my sections and for their helpful advice.

The foregoing paragraphs have dealt with the appearance of tissue in which the hepatic cells have formed cords. Here and there, however, the regenerating cells do not become arranged in columns but lie isolated or in small groups within an otherwise empty stroma. Such cells tend to form multinucleated syncytia (Figs. 27 and 28), or disorderly groups which invade the stroma in a manner faintly suggestive of neoplasia (Fig. 29). Still others form giant tubules reminiscent of those seen at early developmental stages or in the livers of frogs or turtles (Fig. 5).

In most areas the cells of the hyperplastic parenchyma, whether arranged as cords or in isolated groups, have a healthy appearance. There is no evidence of progressive destruction of tissue. But in a few areas the regenerated cells may undergo secondary degeneration, as shown in Figure 35. Here there is a large group of newly formed cells with prominent nuclei which obviously are disintegrating. The tissue is invaded by numerous polymorphonuclear leukocytes.

Among the factors that lead to such secondary destruction are probably ischemia and the accumulation of metabolic products, which are not removed because of stasis of blood and of bile.

Proliferative Changes in the Bile Ducts

Besides regenerative phenomena in the liver cells there are proliferative changes in the bile ducts. Before discussing them it is well to recall that a sharp distinction should be made between interlobular and perilobular (septal) bile ducts.⁴⁰ The former are relatively large, and, together with branches of the portal vein and hepatic artery, lie within a thick mantle of connective tissue. The lining epithelium of these ducts is prominent. At the outskirts of the stroma which enfolds the portal triads, and extending around the lobular peripheries, lie the much smaller septal biliary ducts. Unlike the large interlobular ducts, the smallest septal ducts have a very scanty connective tissue stroma. They are tributaries of the interlobular ducts, and they accompany the fine twigs of the portal veins and hepatic arteries which encircle the lobular peripheries. In the smallest of these minute ducts the epithelium is inconspicuous and so flat that it resembles the lining of the vessels. Even in the larger branches the cells are relatively small and hence the nuclei appear crowded. The cytoplasm stains rather lightly in contrast to the deeply eosin-staining cytoplasm of liver cells; the nuclei are round or oval, and much denser than those of hepatic cells. Into these ducts empty the bile canaliculi of the hepatic cords; the junction usually is expanded into an ampulla.

and the papilla of Vater was available in only 11 cases. In 6 there was inflammatory edema, always associated with edema of the duodenum. The duodenal inflammation was not a localized condition but widespread, involving at times almost the entire gastrointestinal tract.

Lymph Nodes

In nearly all cases, particularly in those in which the duration of hepatitis was less than 1 month, the hepatic, and in many instances the mesenteric, lymph nodes were considerably swollen, their capsules tense, and their cut surfaces bulging and succulent (Fig. 1). Occasionally individual nodes measured as much as 35 mm. in diameter. Microscopically, the sinusoids were dilated and frequently packed with polymorphonuclear cells and macrophages. The reticulo-endothelial lining was prominent. The lymphoid tissue was markedly edematous. In occasional nodes, small foci of necrosis and hemorrhages were encountered. Briefly, the changes in the regional lymph nodes were edema, acute hyperplasia, or acute lymphadenitis, *i.e.*, the usual reactions found near areas of tissue destruction. Involvement of lymph nodes was never generalized.

Ascites

Ascites occurred in 60 per cent of the cases. The amount of fluid usually was large, two or more liters being the average. The fluid was nearly always tinged with bile, less often with blood. Turbidity due to the presence of inflammatory cells was common when phlegmonous inflammation of the gut coexisted (this condition will be discussed later).

The relation between ascites, duration of disease and size of liver is shown in a distribution graph (Text-Fig. 4) and in Table XVII. The weight of the liver has been plotted against duration of disease; cases with ascites are represented by solid circles, those without ascites by open circles. The graph brings out several points. First it shows that ascites may occur at all stages of the disease; no matter whether the course is short or protracted. The occurrence of ascites is not definitely correlated with duration of disease (see Table XVII).

Regarding the relation of size of liver to occurrence of ascites, there is again no apparent correlation. Thus, the incidence of ascites when the liver was greatly shrunken (below 800 gm.) is about the same as when it was enlarged (above 1600 gm.).

In approximately one-fourth of the cases with ascites there was pleural effusion; and in approximately one-half the cases, slight edema of the ankles. The clinical records indicate that ascites precedes ankle

edema, which was probably due to mechanical interference with venous return.

In Bergstrand's⁴¹ series of 95 fatal cases, ascites was observed in 20 per cent. Fox and his co-workers⁴² found ascites in most of their 17 cases.

In summary, it is shown that ascites is common and that it is unrelated to the total duration of the hepatitis or to the size of the liver. The mechanism responsible for the accumulation of abdominal fluid will be discussed later.

Spleen

The spleen was enlarged in about three-fourths of the cases. The weights are given in Table XVIII. In one-third of the series the weight exceeds 300 gm.; in somewhat less than half the weight falls between

TABLE XVIII
Relation of Weight of Spleen to Occurrence of Ascites in 89 Cases of Epidemic Hepatitis

Weight of spleen (gm.)	Number of cases		
	Ascites	No ascites	Total
Below 100	0	1 (1%)	1 (1%)
100—199	10 (11%)	11 (12%)	21 (24%)
200—299	23 (26%)	15 (17%)	38 (43%)
300—399	15 (17%)	6 (7%)	21 (24%)
400—499	2 (3%)	1 (1%)	3 (3%)
500 and over	4 (5%)	1 (1%)	5 (6%)
Total	54 (61%)	35 (39%)	89

200 and 300 gm., in only one-fourth of the cases is the weight approximately normal.

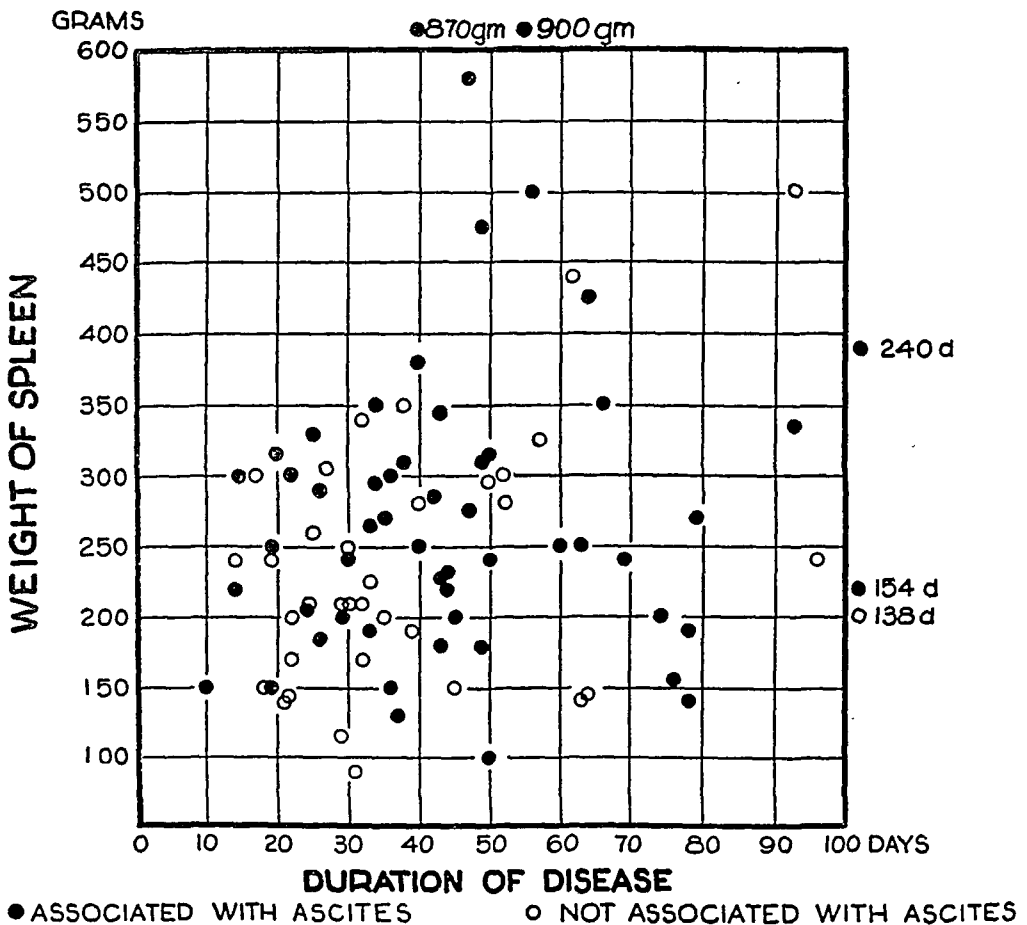
The relation of weight of spleen to duration of hepatitis is shown in Text-Figure 5. There is much scattering but, generally speaking, large spleens, above 300 gm., are more numerous when the disease has been prolonged (see also Table XVIII).

In consistency, the spleen in early cases was flaccid, in later cases, firm. On the cut surface the lymphoid follicles were usually distinct at early stages, and small or indistinct later. At all stages, the blood content of the spleen was increased.

The microscopic appearance also varied with the duration. In relatively early cases, the lymphoid tissue was prominent (Fig. 56); the sinusoidal veins and the pulp cords were only moderately congested. At later stages, the sinusoids were conspicuously distended and had thickened rigid walls (Fig. 57). The lymphoid tissue was often markedly depleted (Fig. 58). The picture then was that usually associated with portal hypertension.

Correlating the gross and microscopic findings, it becomes evident that the enlargement of the spleen in early stages is not the result of engorgement but is predominantly due to a cellular proliferation. At later stages sinusoids become dilated; then swelling is due to engorgement.

The early lymphoid hyperplasia is probably a reaction to products of tissue breakdown in the liver. It cannot be denied, however, that the agent which damages the liver may itself excite a reactive process in the spleen. The depletion of lymphoid tissue, during later stages of hepatitis, may result from portal hypertension, that is, from overload-



Text-Figure 5

ing of the spleen with venous blood under increased pressure.

This interpretation is supported by recent experimental studies of British investigators. Thus Orr⁵¹ studied the spleens of rats, the livers of which had been damaged by "butter-yellow" (a substance which induces a cancerous cirrhosis of the liver). Enlargement of the spleen developed early, long before the liver became cirrhotic. Orr favors

the view that such early enlargement of the spleen is due to cellular hyperplasia. Menon⁵² induced hepatic destruction and late cirrhotic changes by carbon tetrachloride. He found a marked proliferative reaction in the spleen during the early stages of liver damage. Similarly, experiments of Cameron and de Saram⁵³ suggest that splenic changes associated with cirrhosis of the liver (a condition of progressive damage) are the result of two separate processes, namely, pulp hyperplasia and congestion.

Gastrointestinal Tract

Lesions of several kinds and of great interest were encountered in the gastrointestinal tract. The most striking of these was an extensive phlegmonous inflammation with massive edema involving the ileocecal region, less commonly other portions. In addition, noninflammatory edema of both the small and large intestines was frequent, and the lower end of the esophagus was often ulcerated.

Phlegmonous Inflammation

In approximately 15 per cent of the cases in which the gastrointestinal tract was examined (17 of 113), large parts of the gut were phlegmonous. The lesion was usually most marked in the ileocecal region, but sometimes extended more widely, involving the ascending and transverse colon. The wall of the cecum sometimes exceeded 20 mm. in thickness. It was extremely boggy, and its mucosa was thrown into thick folds. The wall of the gut appeared as if artificially injected with a watery fluid (Figs. 48 and 49). Microscopically (Figs. 50 and 51), the entire wall was edematous and everywhere invaded by leukocytes and macrophages. Usually the mucosa was unbroken. Occasionally, superficial hemorrhages were found, but actual erosions were rare. The submucosal layer was especially distended, and even in paraffin sections (in the preparation of which edematous tissue shrinks) exceeded 1 cm. in thickness. The fibers of the mucosa were forced apart, and in some foci appeared to be degenerating. Also the subserosal layer was often considerably distended and invaded by inflammatory cells.

Most of the infiltrating cells had well stained nuclei and intact cytoplasm; they were obviously recent invaders (Fig. 52). The proportion of the cells varied; in some regions polymorphonuclear leukocytes, and in others macrophages, predominated, while lymphocytes and plasma cells were scanty. With stains for bacteria an abundance of small Gram-negative bacteria and larger Gram-positive rods were seen. Coccoid forms were not found. Many of the leukocytes and macro-

phages had ingested these organisms, and some macrophages, particularly, were packed with bacteria.

In nearly all cases, other parts of the small and large intestines were conspicuously edematous, and in some areas the distended tissue showed early inflammatory reaction. In only two cases was a phlegmon found in the stomach.

Without exception, the phlegmonous inflammation was associated with ascites. Careful examination of the clinical records gave no hint of the intestinal lesion. The duration of the phlegmon was always short, as shown by the condition of the exudate; it was evidently a terminal inflammation.

What is the relation between hepatitis and the inflammation of the intestine? The phlegmon gives every appearance of being a terminal event. Therefore it is obvious that the hepatitis is not the result of the intestinal condition. Rather, the phlegmon is a complication which results from invasion by bacteria of an edematous bowel.

In his monograph on yellow atrophy of the liver, Bergstrand⁴¹ merely mentions phlegmonous inflammation of the intestine in several of his autopsy protocols. Recently, Pollack and Gerber⁵⁴ have reported a number of cases, in all of which the lesion was associated with primary disease of the liver. I have been able to find no other references in the literature.

Because intestinal phlegmon is a little known condition, brief abstracts of the anatomic findings in the 17 cases are given below.

ILLUSTRATIVE CASES

Case 8

This patient was a white male, 28 years old. Duration of hepatitis, 43 days. (See page 482 for clinical course.)

Pathologic Findings. *Esophagus:* (G)* superficial ulceration at cardio-esophageal junction; (M)* ulceration; inflammatory reaction extending to muscularis. *Stomach:* (G and M) normal. *Intestine:* (G) marked edema beginning just above ileocecal valve and extending to sigmoid; moderate edema of remainder of small and large intestine. *Duodenum and papilla of Vater:* (M) mucosa normal, intense congestion; submucosa invaded by numerous polymorphonuclear leukocytes and histiocytes. *Cecum:* (M) mucosa intact; wall markedly edematous, dense leukocytic and histiocytic infiltration throughout entire wall; fibrinocellular exudate on serosa.

Case 10

The patient was a white male, 22 years of age. Duration of hepatitis, 30 days.

Pathologic Findings. *Stomach:* (G) mucosa congested; pylorus markedly edematous; (M) marked edema of submucosa. *Duodenum and papilla of Vater:* (G)

* The letter (G) signifies results of gross examination, and (M), of microscopic examination.

extremely marked edema; (M) marked edema; slight leukocytic infiltration; subserous hemorrhages. *Jejunum and ileum*: (G) hemorrhagic; (M) submucosa and subserosa markedly edematous; slightly infiltrated with leukocytes. *Large intestine*: (G) ascending and transverse colon hemorrhagic; (M) mucosa intact; entire wall markedly edematous and heavily infiltrated with polymorphonuclear leukocytes and histiocytes; phlegmon most pronounced in submucosa; serosa showed no reaction.

Case 11

This patient was a white male, 41 years old. Duration of hepatitis, 64 days.

Pathologic Findings. Esophagus: (G) congestion at lower end. *Stomach*: (G and M) multiple petechiae of mucosa. *Small intestine*: (G) moderately edematous; terminal portion of ileum markedly edematous; (M) marked polymorphonuclear, neutrophilic and eosinophilic, infiltration in all layers but particularly of submucosa. *Large intestine*: (G) cecum and first portion of ascending colon: marked edema; subserosal hemorrhages; (M) massive leukocytic and histiocytic infiltration, particularly in submucosa and subserosa.

Case 13

The patient was a white male, 26 years of age. Duration of hepatitis, 49 days. (See page 482 for clinical course.)

Pathologic Findings. Esophagus: (G) congestion of lower third; (M) slight erosion; submucosal scattering of lymphocytes. *Stomach*: (G and M) normal. *Duodenum and papilla of Vater*: (M) moderate submucosal edema; moderate degree of leukocytic and mononuclear cell infiltration in submucosa. *Ileum and jejunum*: (G) normal. *Cecum*: (G) large hemorrhagic areas in submucosa; edema; (M) phlegmonous infiltration.

Case 22

The patient was a white male, 28 years old. Duration of hepatitis, 17 days.

Pathologic Findings. Esophagus and stomach: (G) normal. *Small intestine*: (M) moderate degree of submucosal edema; sparse scattering of histiocytes and lymphocytes. *Large intestine*: (G) cecum was markedly edematous; ascending colon, appendix and terminal ileum not noticeably involved; (M) surface of cecum intact; mucosal glands well preserved; submucosa greatly distended; its thickness exceeded 1 cm.; fibers of muscle layer forced apart; subserosal tissue loosely textured. Throughout submucosa and subserosa, diffuse infiltration with histiocytes and leukocytes. Lower colon had edematous walls, but no cellular exudate had occurred.

Case 29

This patient was a white male, 35 years of age. Duration of hepatitis, 45 days.

Pathologic Findings. Esophagus: (G) superficial erosion; congestion; (M) submucosal edema; foci of lymphocytes and plasma cells. *Stomach*: (G and M) normal. *Duodenum and papilla of Vater*: (G) moderately edematous; slight submucosal edema; sparse scattering of leukocytes. *Ileum and jejunum*: (G) no significant changes. *Large intestine*: (G) almost all portions, but particularly cecum, showed massive edema but no ulceration; (M) mucosa intact; all layers edematous; diffusely infiltrated with leukocytes and histiocytes.

Case 43

The patient was a white male, 24 years old. Duration of hepatitis, 20 days.

Pathologic Findings. Stomach: (G) normal. *Duodenum and papilla of Vater*: (G) no significant changes. *Ileum and jejunum*: (G) no significant changes. *Large*

intestine: (G) mucosa intact; marked congestion and edema; (M) extreme edema and diffuse cellular infiltration throughout all layers; thickness of wall ranged from 8 to 10 mm. Mucosa unbroken; glands normal; supporting stroma infiltrated with scanty numbers of plasma cells, histiocytes and granulocytes. Submucosa the main site of inflammatory edema; its fibers were widely separated and thickly invaded with leukocytes and histiocytes. Venules had collars of exudative cells. In muscular and subserous layers, phlegmonous changes were of somewhat less degree than in submucosa. Muscle fibers in many patches showed degenerative changes.

Case 54

The patient was a white male, 24 years of age. Duration of hepatitis, 36 days.

Pathologic Findings. Stomach and small intestine: (G) hyperemia; (M) moderate degree of edema of small intestine. *Large intestine:* (M) moderate degree of edema and phlegmonous inflammation, most marked in submucosa and subserosa.

Case 55

This patient was a white male, 23 years old. Duration of hepatitis, 29 days.

Pathologic Findings. Esophagus: (M) two superficial ulcers at cardiac end; subjacent tissue edematous and massively infiltrated with lymphocytes and leukocytes; base of ulcer covered with fibrin. *Stomach:* (G) multiple petechiae. *Small intestine:* (G) multiple petechiae. *Large intestine:* (G) marked edema, particularly of cecum and ascending colon; multiple petechiae; (M) mucosa preserved; extensive phlegmonous infiltration, particularly of cecum.

Case 59

The patient was a white male, 26 years old. Duration of hepatitis, 38 days. (See page 493 for clinical course.)

Pathologic Findings. Esophagus: (G) no significant changes. *Stomach:* (M) edema of submucosa; scattered inflammatory cells. *Duodenum:* (G) slight edema. *Ileum:* (G) lower portion markedly edematous but not congested. *Large intestine:* (G) cecum, ascending and transverse colon; intense edema; no congestion; (M) diffuse phlegmonous infiltration of cecum and ascending colon; remainder of colon edematous.

Case 61

The patient was a white male, 25 years of age. Duration of hepatitis, 40 days.

Pathologic Findings. Esophagus: (G) several small longitudinal erosions in lower third. *Stomach:* (G) multiple superficial ulcers. *Duodenum and papilla of Vater:* (G) edematous; congested. *Ileum and jejunum:* (G) edematous. *Large intestine:* (G) marked edema, especially in sigmoid; here wall averaged 1 cm. in thickness, section had a yellowish gray appearance; mucosa preserved; (M) entire wall densely and diffusely infiltrated with granulocytes, including many eosinophils, and macrophages; exudate most conspicuous in submucosa but all layers crowded with cells; in appendix, same changes but less marked.

Case 94

This patient was a white male, 35 years of age. Duration of hepatitis, 50 days.

Pathologic Findings. Esophagus and stomach: (G and M) no significant changes. *Duodenum and papilla of Vater:* (G) wall very edematous; mucosa hyperemic. *Jejunum:* (G) slightly edematous; mucosa congested. *Large intestine:* (G) walls very soggy; mucosa not ulcerated; (M) mucosa intact; submucosa extremely edematous with numerous leukocytes and histiocytes; remainder of wall moderately edematous and diffusely infiltrated with inflammatory cells. *Ileum:* (G)

moderately edematous; (M) edematous; wall diffusely infiltrated with leukocytes and histiocytes.

Case 97

The patient was a white male, 50 years old. Duration of hepatitis, 74 days.

Pathologic Findings. Esophagus: (G) no significant changes. *Stomach:* (G) moderately edematous; (M) edema; scattered histiocytes in submucosa and muscularis. *Small intestine:* (G) walls thickened and moist; (M) moderate edema of submucosa and serosa; scattered histiocytes in subserous layer. *Large intestine:* (G) wall thickened and markedly edematous; mucosa thrown up in folds, giving a coarse nodular appearance; (M) marked edema of entire wall with diffuse infiltration of granulocytes, histiocytes, lymphocytes and plasma cells; process was most marked in submucosa and muscularis.

Case 100

This patient was a white male, 27 years of age. Duration of hepatitis, 93 days. (See page 485 for clinical course.)

Pathologic Findings. Esophagus, stomach and small intestine: (G) no significant changes. *Large intestine:* (G) appendix was normal; wall of ascending colon markedly edematous; no ulceration; (M) conspicuous edema of submucosa and infiltration with histiocytes, granulocytes and plasma cells.

Case 103

This patient was a white male, 22 years old. Duration of hepatitis, 49 days.

Pathologic Findings. Esophagus: (G) no gross ulceration; surface discolored by reddish black material; (M) superficial ulceration with conspicuous polymorphonuclear and histiocytic reaction; underlying tissue slightly edematous and sparsely infiltrated with inflammatory cells. *Stomach:* (G) multiple petechiae; (M) no significant changes. *Duodenum and papilla of Vater:* (G) congestion of mucosa. *Jejunum and ileum:* (G) intense congestion of mucosa; (M) congestion. *Large intestine:* (G) normal; (M) edema of submucosa; diffuse infiltration with leukocytes and histiocytes.

Case 107

The patient was a white male, 26 years of age. Duration of hepatitis, 50 days.

Pathologic Findings. Stomach: (G) no significant changes. *Duodenum:* (M) diffuse sprinkling of lymphocytes, histiocytes and occasional eosinophile cells throughout all layers. *Ileum and jejunum:* (G) no noteworthy changes. *Large intestine:* (G) normal; (M) edema of submucosa, diffuse infiltration with granulocytes and histiocytes.

Case 112

This patient was a white male, 38 years old. Duration of hepatitis, 40 days.

Pathologic Findings. Esophagus, stomach and small intestine: (G) no significant changes. *Large intestine:* (G) subserosal hemorrhages in descending colon and sigmoid; (M) marked edema; diffuse inflammatory reaction throughout wall; mucosa intact.

Noninflammatory Edema of the Intestine

In addition to the 17 cases with phlegmon, there was noninflammatory edema of small and large intestines in 26 other cases. The edema varied in degree, and involved especially the submucosa (Fig. 53). In all of the cases there was associated ascites.

Ulceration of the Esophagus

The lower one-third of the esophagus in many cases showed changes such as are frequently regarded as due to post-mortem autolysis. The mucosal surface had partly sloughed away, and there were small longitudinal erosions, often covered by chocolate brown débris. Because these lesions are so commonly looked upon as post-mortem changes, material for histologic examinations was available in only 20 cases. In 9 of them, there was superficial ulceration, accompanied by an inflammatory reaction that usually extended to the muscularis, and more rarely throughout the entire wall. The appearance in a representative case is shown in Figure 54. Here, small superficial erosions were present at the cardio-esophageal junction. The denuded tissue was the site of an acute inflammatory reaction that extended laterally beyond the eroded portions and down to the muscularis.

Erosion of this type is too well known to merit further description. It probably occurred more often in the present series than the figures indicate. Most writers on the subject agree that the action of the gastric juice plays an important part in the pathogenesis of esophageal ulceration.⁵⁵⁻⁵⁷ It is when vomiting is protracted that erosions occur. Even nausea, without vomiting, by relaxation of the cardiac sphincter and regurgitation of gastric juice may induce the lesion. Nausea and vomiting alone, however, are not sufficient; poor circulation in the esophagus, and a state of debilitation of the patient appear to be prerequisites. These factors—nausea, protracted vomiting, debilitation and, probably, impaired circulation in the esophagus (due to interference with the circulation through the liver)—are found in nearly all fatal cases of epidemic hepatitis.

Hemorrhagic Phenomena

As in other forms of hepatic disease, hemorrhages were found in epidemic hepatitis. The location of the hemorrhages in 109 cases is shown in Table XIX. Microscopic hemorrhages are not included in this tabulation. Most common were hemorrhages in the intestinal tract,

TABLE XIX
Location of Hemorrhages in 109 Cases of Epidemic Hepatitis

Location	No. of cases	Per cent of cases
Intestines or mesentery	80	73
Lungs	74	68
Heart	43	39
Kidney	14	13
Skin	8	7
Brain	5	5

which occurred in approximately three-fourths of the series. In degree, they varied from petechiae beneath the serosa and in the mucosa to larger hemorrhages, which were usually at the attachment of the gut to the mesentery or mesocolon (Fig. 63).

Almost as frequent were hemorrhages in the lungs, in which dark red, almost black, hemorrhagic patches with ill-defined outlines were scattered through all lobes. The bronchial walls were dusky red. Sometimes the supporting tissue around the larger vessels was hemorrhagic. Microscopically, in large areas the air sacs and bronchial walls were flooded with blood. It is probable that the pulmonary hemorrhages predispose to bacterial invasion, for in a great majority of cases foci of terminal pneumonia were found at autopsy.

Next in frequency were hemorrhages in the heart, where they were located in the epicardium and, commonly, beneath the septal endocardium of the left ventricle, near the undefended space (Fig. 62).

In the kidney, the hemorrhages were usually pelvic in location. In other organs hemorrhages were found more rarely.

Bone Marrow

Bone marrow specimens were available for histologic examination in 22 cases, the tissue having been selected usually from rib, sternum, or vertebra. This relatively small series fortunately represents early cases, cases of average duration and others with a protracted course. When one takes into consideration the variables dependent on the age of the patient and the site of the particular specimen, certain generalities can be established.

In most instances there was a mild to moderate degree of hyperplasia (Fig. 64) due more to increased activity of the erythrocytic than of the granulocytic series. Megakaryocytes were normal in structure and distribution and varied in number with the degree of general hyperplasia. There was no disturbance of maturation in the several developmental series, and most cells were found in the midstage (*i.e.*, erythroblasts, myelocytes) or beyond. Degenerative changes were not evident. Pigment, presumably hemosiderin, was often noted within histiocytes.

Certain cases displayed maximal hyperplasia, fat being completely replaced by hematopoietic tissue, which in some instances was predominantly erythroid (Fig. 66), in others myeloid (Fig. 65). The changes bore no constant relation to length of disease. They suggest, however, that a certain degree of hyperplasia of bone marrow occurs at all stages of fatal epidemic hepatitis, probably as the combined result of hemorrhages and of hepatic destruction.

Kidneys

In the majority of cases the kidneys were swollen, flaccid, and bile-stained. The combined weights, tabulated in 88 cases, are as follows: Below 300 gm., 1 case; 300 to 399, 25 cases; 400 to 499, 36 cases; 500 to 599, 17 cases; over 600 gm., 9 cases. The kidneys were therefore considerably swollen, *i.e.*, they weighed over 400 gm. in 70 per cent of the cases. Microscopically, the lesions in most of the kidneys were typical of cholemic nephrosis. The glomeruli were well filled and normally cellular. Precipitated protein in the capsular space, frequently present, indicated alterations in permeability of the filtering capillaries. Pigmented casts lay in the lumina of various parts of the tubular system, particularly in the distal convoluted and the collecting tubules (Fig. 59). Degenerative changes of varying degree were evident, ranging from simple "cloudy swelling" to actual necrosis similar to that of mercurial poisoning (Fig. 60). In severely damaged kidneys, regeneration seemed to go hand in hand with destruction, and it was common to see tubules relined by flat epithelium (Fig. 61).

Cholemic nephrosis has received much less attention than the condition merits.⁵⁸⁻⁶⁰

Testis

Cirrhosis of the liver is not infrequently associated with atrophy of the testis. It is therefore a matter of much interest to examine this organ in cases of fatal epidemic hepatitis. Material was available in 38 cases. In 7 cases the organs were found to be completely atrophic and fibrotic: in 5 some degree of disturbance of spermatogenesis was evident, and in 26 cases the testes were normal. In the 7 cases of complete atrophy and fibrosis, the duration of hepatitis was from 26 to 64 days. The testicular process in all appeared to be of much longer duration.

In the 5 cases in which there was a varying degree of interference with spermatogenesis, there was some edema of stroma but without fibrosis. Hepatitis had been present from 52 to 76 days in 4, and 138 days in one. In these cases it is not certain whether the testicular changes can be related to the hepatic damage.

It may here be pertinent to recall the relation of the liver to the testis. The liver is important in the metabolic disposal of sex hormones. When, because of hepatic insufficiency, this disposal does not take place, estrogens accumulate; these substances, in excessive concentration, very probably damage the sperm-forming cells of the testis and thus may lead to severe atrophy.⁶¹

In a recent study of 34 cases of hepatic failure other than cirrhosis (carcinoma, amyloidosis, hemochromatosis) Morrione⁶² found that in

order to result in atrophy of the testis, damage in the liver must be severe, extensive and long-standing. Whether in any case of the present series the testicular damage can be related to the hepatic damage is doubtful. Study of much additional material is required to aid in the solution of this complicated problem.

Brain

Grossly, the brain showed little alteration, except edema. In 62 cases, blocks from representative areas were available for microscopic examination. The changes found were of two kinds. One was acute degeneration of ganglion cells, the other inflammatory reaction around vessels and in the meninges.

The changes in the ganglion cells were of types such as occur commonly in many different diseases (Figs. 67 to 69). Satellitosis around damaged cells was rare. The ganglion cell changes were irregular in distribution; no part of the brain was especially affected. Occasionally, isolated cells were completely destroyed; their remnants usually were invaded by glial elements (Figs. 70 and 71). In a few instances there were found tiny glial nodules (Fig. 72). Otherwise, glial reactions of any kind were sparse.

The vessels had normal walls; hemorrhages were rare. Edema of varied degree was usually present. There were nowhere any areas of demyelination. All these changes are nonspecific.

A different and more important lesion was found in the basal meninges and around the vessels of the brain stem (including the hypothalamus), in the periventricular system and the nucleus basalis. In these regions occasional small vessels were cuffed by lymphocytes (Fig. 73). Such perivascular infiltration was never pronounced. Figure 74 is representative of the average degree. The meninges showed a similar and often more diffuse lymphocytic infiltration (Figs. 75 and 76). The vessel walls were never necrotic. The lesions did not occur in the cortex or the subjacent white matter.

The perivascular and meningeal infiltrations were present in approximately 15 per cent of the brains examined. The lesions are sufficient in degree to be considered a mild meningo-encephalitis.

PATHOLOGIC PHYSIOLOGY OF FATAL EPIDEMIC HEPATITIS

It is beyond the scope of this paper to discuss all of the varying functional faults encountered in fatal cases of epidemic hepatitis. Rather, I shall briefly discuss the mechanism underlying the jaundice, the ascites, the hemorrhagic phenomena and the cerebral manifestations.

Jaundice

Jaundice indicates a disturbance of the balance between the rates of bile pigment production and its excretion by liver cells into the biliary system. Regarding the pathogenesis of jaundice there are two main schools. By one, following the teaching of McNee,⁶³ three types of jaundice are recognized: hemolytic jaundice, toxic jaundice and obstructive jaundice. In hemolytic jaundice the rate of bile pigment formation, due to excessive destruction of red corpuscles, is so great that it exceeds the rate with which the liver cells can modify and then eliminate the pigment. Hence, an excess of bilirubin accumulates in the circulation and tints certain tissues. In the second type of jaundice, the toxic variety, the liver cells are severely damaged or actually killed and hence cannot take up the bilirubin of normal hemoglobin breakdown from the circulating blood. In the third type, obstructive jaundice, the rate of pigment formation by the reticulo-endothelial cells is normal and the liver cells are able to secrete the pigment into the intracolumnar canaliculi. Due to obstruction somewhere in the excretory duct system, the delicate canaliculi become distended beyond their capacity and rupture, spilling bile into the space of Disse or directly into the circulating blood.

A somewhat different view concerning the mechanism of jaundice is expressed by Rich.⁶⁴ He recognizes only two main types: retention jaundice and regurgitation jaundice. The former is practically synonymous with hemolytic jaundice of other writers. It occurs in various anemias and in any condition associated with increased destruction of red blood cells. The other form, regurgitation jaundice, is due to a reflux of bile from the intralobular canaliculi into the blood stream. It results from rupture of the delicate canaliculi, brought about either by necrosis of liver cells or by obstruction of the outflow of bile anywhere within the biliary system. The regurgitation jaundice of Rich, therefore, includes both the toxic and obstructive variety. He believes catarrhal jaundice to be a form of regurgitation jaundice of unknown pathogenesis.

McNee, Rich, and other students of jaundice agree that the causes of jaundice cannot always be placed in these separate compartments; there is often a combination of several factors.

Catarrhal jaundice for many years was thought to be due to obstruction at the lower end of the biliary duct system. In contrast, the jaundice of idiopathic yellow atrophy of the liver—a condition formerly regarded as an unrelated disease—was usually attributed to damage or destruction of liver cells. It has been shown, however, that catarrhal jaundice and yellow atrophy of the liver are not different diseases but

different forms of the same disease, namely, epidemic hepatitis. If this be true, then it may be expected that in both forms the pathogenesis of jaundice is the same. Actually, in both forms, the cause of jaundice appears to lie principally in obstruction of the intralobular canaliculi by bile thrombi. In biopsies reported by Scandinavian and British investigators, and in rare post-mortem examinations of patients who have died from accidental causes, the liver in catarrhal jaundice has always shown, within bile canaliculi, plugs of altered and inspissated bile. In fatal cases of epidemic hepatitis, *i.e.*, in "idiopathic" yellow atrophy, these plugs occur in great numbers within the intralobular canaliculi. In contrast the extralobular ducts, small and large, are patent. No doubt, injury to the liver may be an additional factor in early stages of epidemic hepatitis in both its benign and malignant forms. But it is more than probable that mechanical obstruction of the intralobular canaliculi is the most important cause of the persistent jaundice of epidemic hepatitis.

Ascites

Ascites is a common event in fatal epidemic hepatitis. It occurs in approximately two-thirds of the cases. Most often ascites appears rather suddenly, during the final phase of the disease. It should be emphasized, however, that it may occur also, though less often, in patients who recover.

The mechanism of ascites is complex. At least two factors are usually involved: (1) alteration of the plasma proteins which leads to lowering of the colloid osmotic pressure, and (2) increase in portal blood pressure due to interference with venous flow through the liver. The resulting states will, in turn, bring about anoxic increase in capillary permeability.

It is well known that extensive damage to the liver tends to lower the quantity of the plasma proteins and alter their relative proportion.⁶⁵ In many cases of this series, the plasma proteins were depleted. Ascites, however, often appeared before the protein level dropped. This was especially true when the course of hepatitis was rapid. In a considerable number of cases the plasma proteins showed little alteration. Moreover, the accumulation of fluid was commonly limited to the abdominal cavity; general edema was rare. There is, however, no constant relation between the level of plasma proteins and the colloid osmotic pressure of the blood. This subject was discussed in a recent paper by Butt, Snell and Keys.⁶⁶ These investigators brought together experimental and clinical evidence which indicates that in hepatic disease the proteins may be altered both in quantity and in quality.

They were unable to demonstrate a constant "edema level" by measuring the colloid osmotic pressure. They cited the results of unpublished experiments of Bollman, who found no direct relation between the appearance of ascites and any exact serum protein concentration or level of the colloid osmotic pressure. But Bollman did find the rapidity of appearance of ascites more directly related to the extent of the hepatic injury. All these facts suggest that fall in the plasma proteins or in osmotic pressure is usually not the main cause of ascites in fatal epidemic hepatitis.

We may now consider another factor that may be responsible for ascites, namely, obstruction to the flow of blood in the liver. In epidemic hepatitis many efferent veins are severely injured. There is marked endophlebitis, sometimes thrombosis and complete obliteration. Moreover, there are changes in the distribution of blood within the liver. Where new parenchyma has been formed the tissue is markedly ischemic. Where tissue has been destroyed there is great engorgement, perhaps stagnation. There is, therefore, the possibility that even in early stages of hepatitis portal flow may be impaired.

That portal obstruction actually exists is shown by comparison of spleens from patients with ascites and from those without ascites. The spleen in the ascitic group is enlarged twice as often as in the group without ascites. This enlargement may be regarded as evidence of portal obstruction. Although this does not furnish positive proof, it suggests that obstruction to portal flow is at least one factor in the pathogenesis of ascites.

Besides mechanical obstruction, other factors may be concerned. The liver normally stores a large proportion of ingested water.⁶⁷ Destruction of much of the parenchyma in fatal hepatitis may interfere with the function of water storage and thus contribute to the establishment of ascites.

Hemorrhagic Phenomena

The hemorrhagic phenomena of epidemic hepatitis are doubtless due to disturbance in prothrombin formation in the damaged liver. The relation of hemorrhage to liver damage has been reviewed in recent papers.^{68, 69}

Cerebral Manifestation

Mental and nervous manifestations are almost invariably present during the final phase of fatal hepatitis. These are somewhat paralleled by the symptoms observed in experimental animals subjected to complete removal of the liver. In such animals the symptoms produced, and the death of the animals, must be attributed chiefly to hypoglycemia which takes places after the liver, the chief storehouse of

glycogen, is removed. However, animals in which some hepatic tissue remains do not show the typical symptoms that are present when the liver is removed completely. Death in such animals cannot always be attributed to hypoglycemia.⁶⁵

Severe hepatic injury must inevitably lead to serious disturbances in the chemical composition of the body fluids, on the stability of which depends the normal state of all tissue. It seems reasonable to assume that it is the general imbalance of tissue fluids rather than the disturbance of a single component, such as sugar, which is responsible for the cerebral manifestations and for death.

The anatomic background of the cerebral symptoms is ill-defined. In this series, two main kinds of changes were found on microscopic examination. One was acute nonspecific degeneration of ganglion cells, such as accompanies many different diseases. These changes occurred in all cases. The other was a mild form of meningo-encephalitis located particularly in the brain stem, including the hypothalamus, the periventricular system and the nucleus basalis; the cortex and the subjacent white matter remained untouched. These changes occurred in approximately 15 per cent of the brains.

The lesions are different from those found in virus diseases, such as measles, mumps, or vaccinia. In these, foci of demyelination and often necrosis of small arteries are characteristic; such alterations are not found in cases of hepatitis.

The cerebral symptoms of hepatitis have some points in common with Wernicke's syndrome, in which the clinical manifestations are lethargy or drowsiness terminating in coma, and sometimes periods of excitement. Frequently, these nervous manifestations are associated with vomiting.⁷¹ In the pathogenesis of Wernicke's syndrome, vitamin deficiency, particularly deficiency in Vitamin B₁, is thought to play an important part. Deficiencies of several vitamins probably occur when the liver is as extensively damaged as it is in fatal hepatitis. However, anatomically the lesions of Wernicke's encephalopathy differ from those found in cases of epidemic hepatitis. In Wernicke's encephalopathy the lesions consist mainly of vascular proliferations, a varying degree of glial proliferation, and absence of perivascular lymphocytic cuffing.^{70, 71} In hepatitis, on the other hand, vascular and glial proliferations are inconspicuous or absent, but perivascular lymphatic infiltration is present. Because of these differences there is no ground for believing that the cerebral lesions of hepatitis are the result of vitamin B₁ deficiency.

We may now consider whether the changes in the brain may result from toxic substances passing through the damaged liver. The portal

blood always contains an abundance of toxic products of digestion which in the normal liver are detoxified. Through the greatly damaged liver of fatal hepatitis they may pass unaltered. Certain experiments of Baló and Korpássy⁷² have a bearing on this point. When dogs with Eck's fistula were fed meat, 6 of 8 animals presented symptoms of encephalitis. In the brains of 3 dogs, histologic changes were found which corresponded to nonsuppurative encephalitis; they were located particularly in the striate body. These lesions were of similar kind, but of greater degree, than those found in hepatitis. Baló and Korpássy concluded that the encephalitis in their experimental animals was due to intoxication caused by exclusion of the liver.

It seems probable that in fatal hepatitis the detoxifying function of the liver is so altered as to permit the circulation of substances normally bound or destroyed in this organ. The working hypothesis is proposed that the cerebral changes of hepatitis result chiefly from loss of the detoxifying function of the liver.

SUMMARY

This study is based upon 125 fatal cases of hepatitis which occurred in the U. S. Army during the epidemic of 1942.

In an historical summary it has been shown that hepatitis is not a new disease; many epidemics have occurred. In all epidemics the clinical picture has been remarkably similar. The mortality has always been low, from 0.2 to 0.4 per cent.

Prior to World War I there was little information concerning the lesions of epidemic hepatitis. It has gradually come to be recognized that the lesions in the livers of fatal cases correspond to those long known as idiopathic acute yellow atrophy. Nevertheless, the view that yellow atrophy and epidemic hepatitis are but two extremes of the same disease has not been accepted by all. The present studies leave little doubt that idiopathic yellow atrophy represents the end stage of fatal epidemic hepatitis.

The clinical course in the fatal cases has been analyzed. There were three distinct phases: pre-icteric or initial, intermediate, and final. In the great majority, the initial phase lasted 7 days or less, the intermediate phase no more than 26 days, the final phase no more than 10. The initial symptoms were the same as those in cases of the nonfatal disease. The intermediate phase began with the onset of jaundice; during its early stages there was no indication that the disease was not going to run its usual benign course. However, in the majority there was a sudden dramatic change which initiated the final phase of the disease; it usually was marked by the development of cerebral manifestations, persistent vomiting and ascites. The cerebral symptoms

were, principally, lethargy and coma alternating with excitement and delirium.

The patient was usually afebrile, except during the terminal stage. The pulse was rarely slow. The blood pressure was normal, except during periods of excitement in the final phase.

During the stages preceding the final phase the liver was usually enlarged and tender. Later it shrank rapidly.

As the disease progressed, moderate anemia appeared. In all but the final stage, there was usually slight leukopenia with relative lymphocytosis.

The chief lesions were found in the liver. They were those typical of yellow atrophy. Characteristically, involvement of the liver was not uniform. In large areas all the parenchyma was destroyed, leaving only skeletal remnants of the lobules, whereas elsewhere destruction was incomplete. The remains of lobules were outlined by small proliferating bile ducts. The destruction affected only the liver cells, the framework and sinusoids remaining unaltered. Scarring did not occur. It is characteristic of the destructive process that the dead cells were removed rapidly. In the areas of destruction there was an inflammatory reaction that persisted for a long time. Macrophages filled with lipofuscin were particularly prominent. The efferent veins were the site of marked endophlebitis.

Hyperplasia of surviving cells led to the formation of much new tissue which grossly appeared coarsely nodular or tumor-like. Microscopically, this tissue almost never had a normal lobular structure. The new parenchyma was formed almost exclusively from pre-existing liver cells. However, there is some morphologic evidence that liver cells are sometimes derived from bile ducts. While it is impossible to decide on morphologic grounds whether bile ducts can actually form liver cells, it is probable that they do so.

The newly formed parenchyma was markedly ischemic and overlaid with bile, due to obstruction in the intralobular canaliculi. The extralobular bile ducts were normal. There was no evidence of progressive destruction of tissue. But in some areas the newly formed parenchyma degenerated because of ischemia, bile stasis, and, perhaps, accumulation of metabolic waste products.

The gallbladder showed no significant change.

The regional lymph nodes of the liver were edematous and often hyperplastic.

The spleen in the majority of instances was enlarged. In early stages, enlargement was due to cellular proliferation, and in later stages to congestion.

The bone marrow usually was moderately hyperplastic.

In the gastrointestinal tract edema was commonly found, and in about 15 per cent of the cases there was a phlegmonous inflammation, particularly in the cecal region. The phlegmon was probably a late event, as the inflammatory cells were well preserved.

The kidney usually showed the picture of cholemic nephrosis.

In the brain two kinds of changes were present: an acute nonspecific degeneration of ganglion cells, and a mild meningo-encephalitis which occurred in about 15 per cent of the cases.

Hemorrhages were found particularly in the lung, intestine, epicardium, endocardium and kidney. Hemorrhagic phenomena may be attributed to disturbances in vitamin-K metabolism and to changes in the level of prothrombin, both due to destruction of liver.

Ascites occurred in two-thirds of the cases; its frequency was unrelated to the total duration of hepatitis. It usually developed late in the disease. Ascites is thought to be due principally to interference with blood flow through the liver, although other factors may be concerned, such as change in plasma proteins and interference with the water-storage capacity of the liver.

The mechanism of jaundice is believed to be obstruction of the intralobular canaliculi.

The cerebral lesions are believed to be due to loss of the detoxifying function of the liver, although here, too, the exact mechanism is not known.

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[Illustrations follow]

DESCRIPTION OF PLATES

PLATE 88

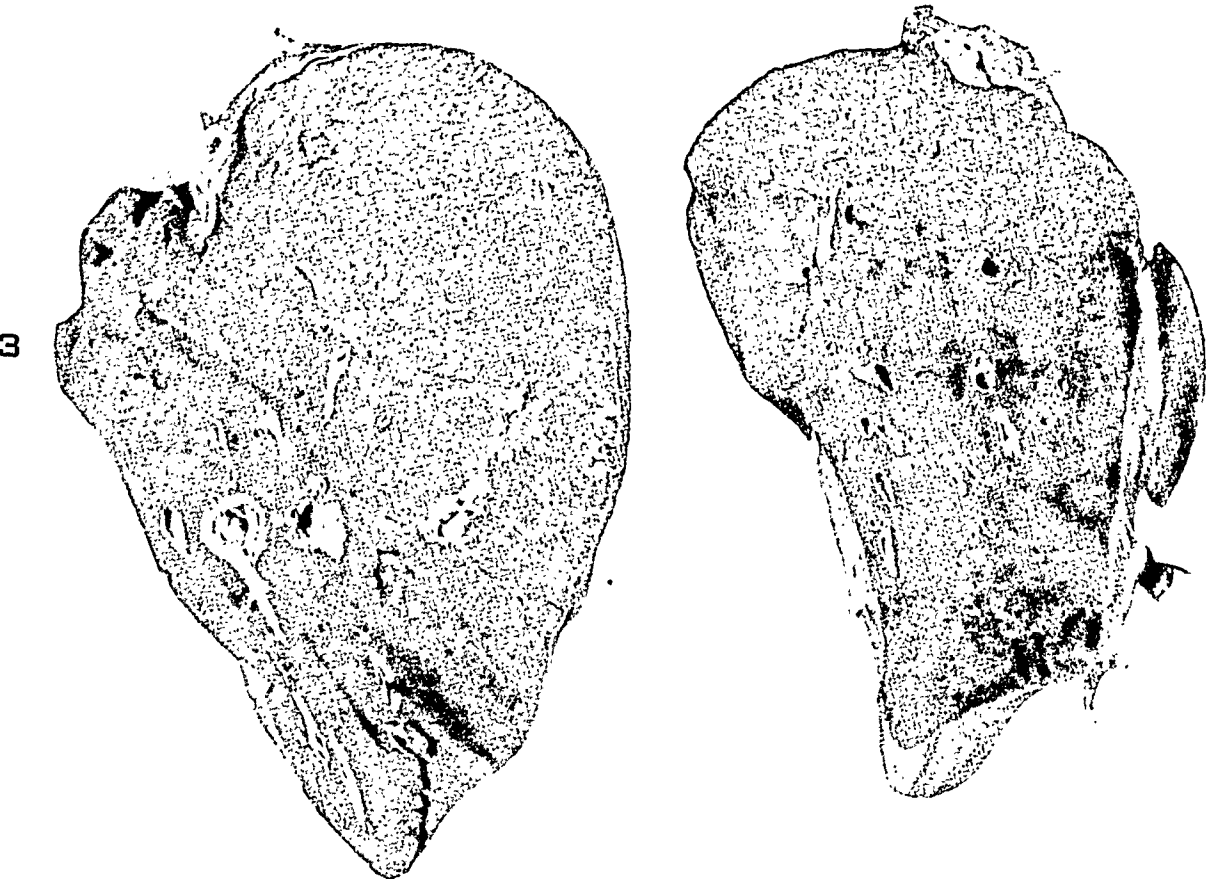
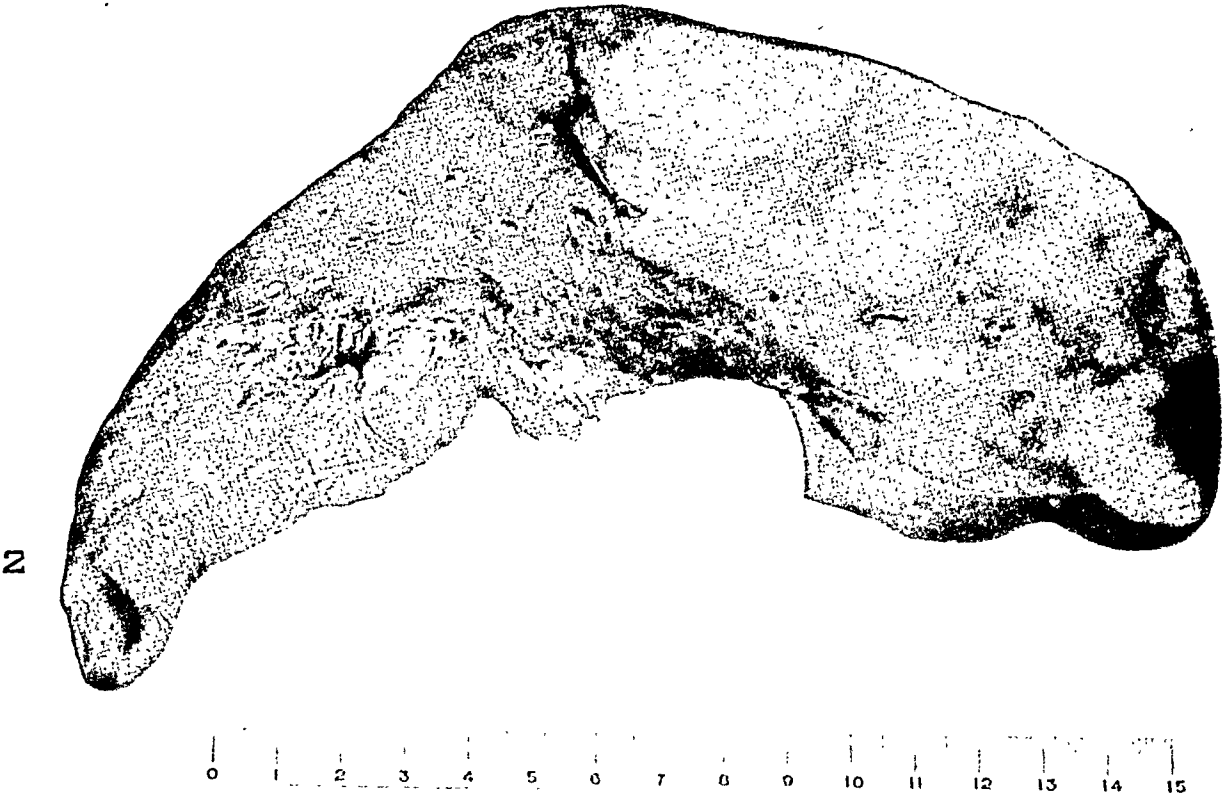
FIG. 1. Case 24. Duration of hepatitis, 36 days. Under surface of a liver which weighed 1320 gm. The liver is shrunken, particularly the left lobe. The surface of the right lobe shows a number of flat or elevated nodular areas, between which the tissue is finely wrinkled. The surface of the left lobe is deeply furrowed. At the hilum is a cluster of enlarged, edematous lymph nodes. (For microscopic appearance of liver see Fig. 30; hemorrhages in heart and gut of this case are shown in Figs. 62 and 63.)



PLATE 89

FIG. 2. Case 81. Duration of disease, 19 days. Cut surface of a liver which weighed 890 gm. Over one-half of the organ has a fleshy, red appearance: here all liver cells have been destroyed. The yellow nodular patches are relatively ischemic, and are composed of large "lobules" of regenerating tissue. (The microscopic appearance of the red part is shown in Fig. 4.)

FIG. 3. Case 8. Duration of disease, 43 days. Vertical cut section of a liver which weighed 850 gm. The large, red, fleshy area consists entirely of vascular stroma and bile ducts; all liver cells have been destroyed. The remainder of the organ is composed of yellowish green nodular areas of regenerating parenchyma. (The microscopic appearance of the latter is shown in Figs. 27 and 28. For microscopic appearance of the esophagus from this case see Fig. 54.)



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PLATE 90

- FIG. 4. Case 81. Duration of disease, 19 days. Microscopic appearance of the red, fleshy area of the liver shown in Fig. 2. The parenchyma has been destroyed. The lobular outlines are indicated by numerous, small, biliary ducts. The sinusoids are greatly engorged. Masson's trichrome stain. $\times 250$.
- FIG. 5. Case 84. Duration of disease, 93 days. Microscopic appearance of the pale nodular areas of regenerative hyperplasia shown in Fig. 11. Cords of liver cells form a pseudolobule which is noticeably ischemic. Elsewhere small bile ducts and large tubules composed of hepatic cells are scattered throughout the collapsed stroma; these large tubules are reminiscent of the liver in the early stage of embryonic development. $\times 250$.
- FIG. 6a. Case 115. Duration of disease, 18 days. Numerous macrophages with yellow-brown granules are scattered throughout the lobular stroma from which the liver cells have been removed. $\times 500$.
- FIG. 6b. A section from an area similar to the one shown in Figure 6a, but stained with Sudan III. The pigment granules take the fat stain well. $\times 500$.

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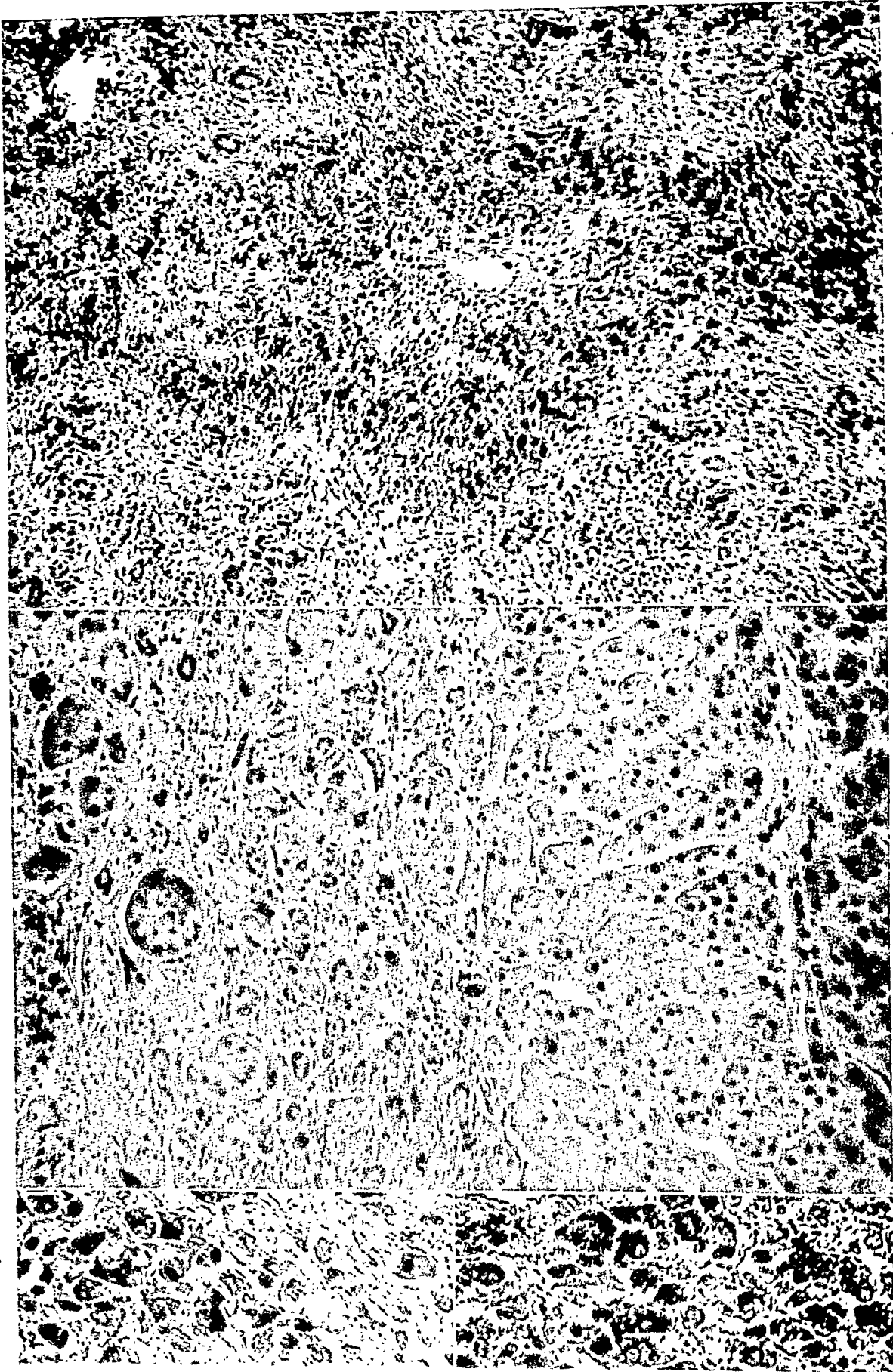
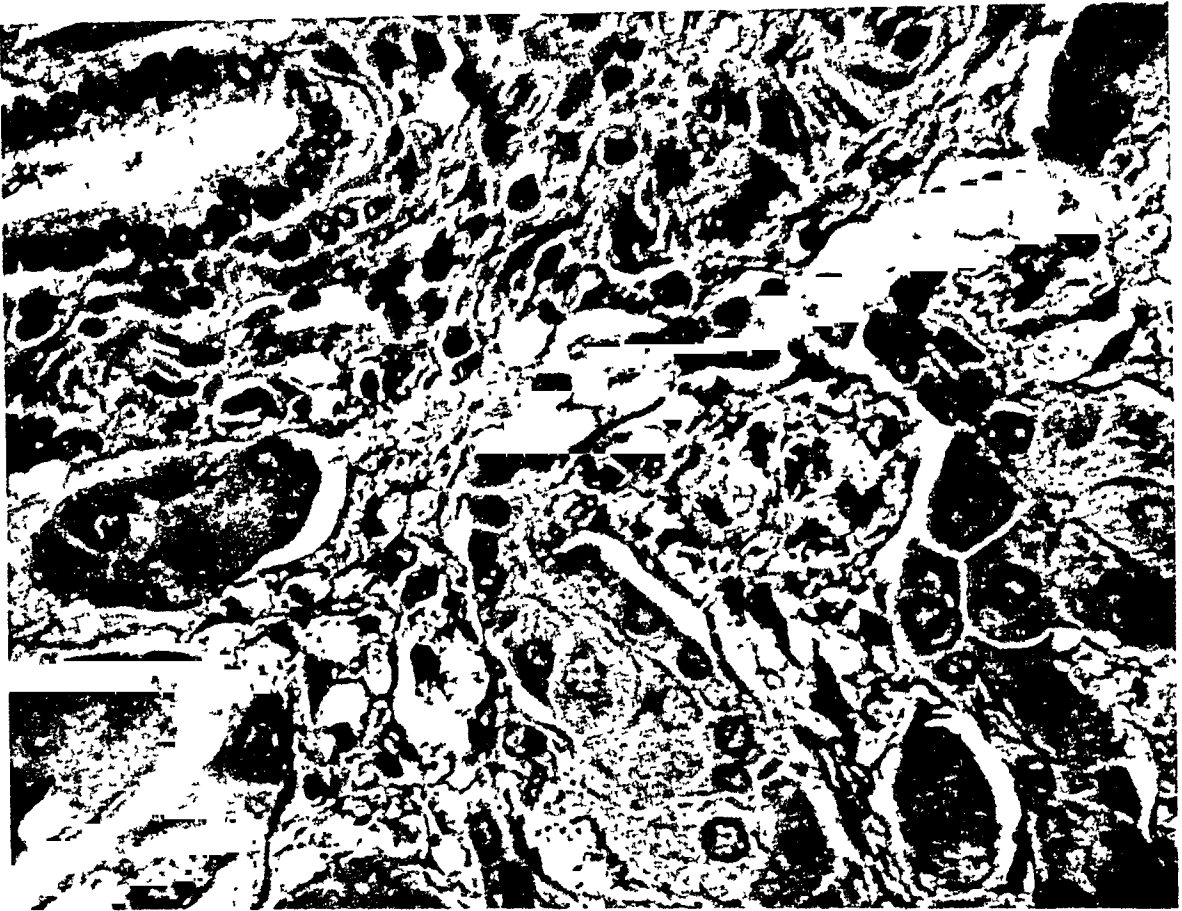


PLATE 91

- FIG. 7. Case 104. Duration of disease, 98 days. A branching bile duct, the lumen of which is in continuity with the canaliculi of two atypical and probably regenerated hepatic columns. This appearance suggests a possible transformation of biliary epithelium into liver cells. $\times 650$.
- FIG. 8. Case 28. Duration of disease, 21 days. The lumen of a branching bile duct is continuous with that of a tubule composed of liver cells. Surrounded by the epithelium of the bile duct lie several large typical liver cells; as in Figure 7, this suggests a transformation of biliary cells into hepatic cells. The section comes from an area of "red atrophy." $\times 650$

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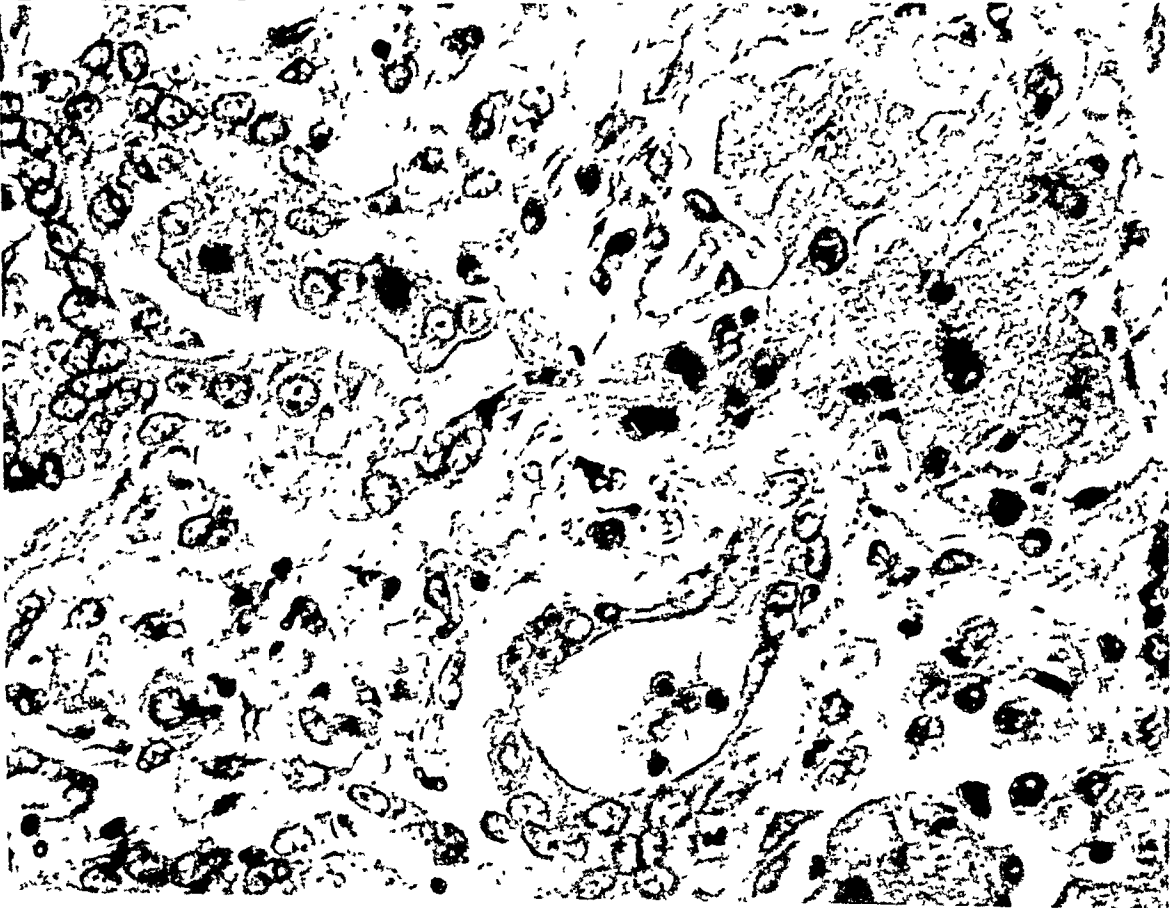
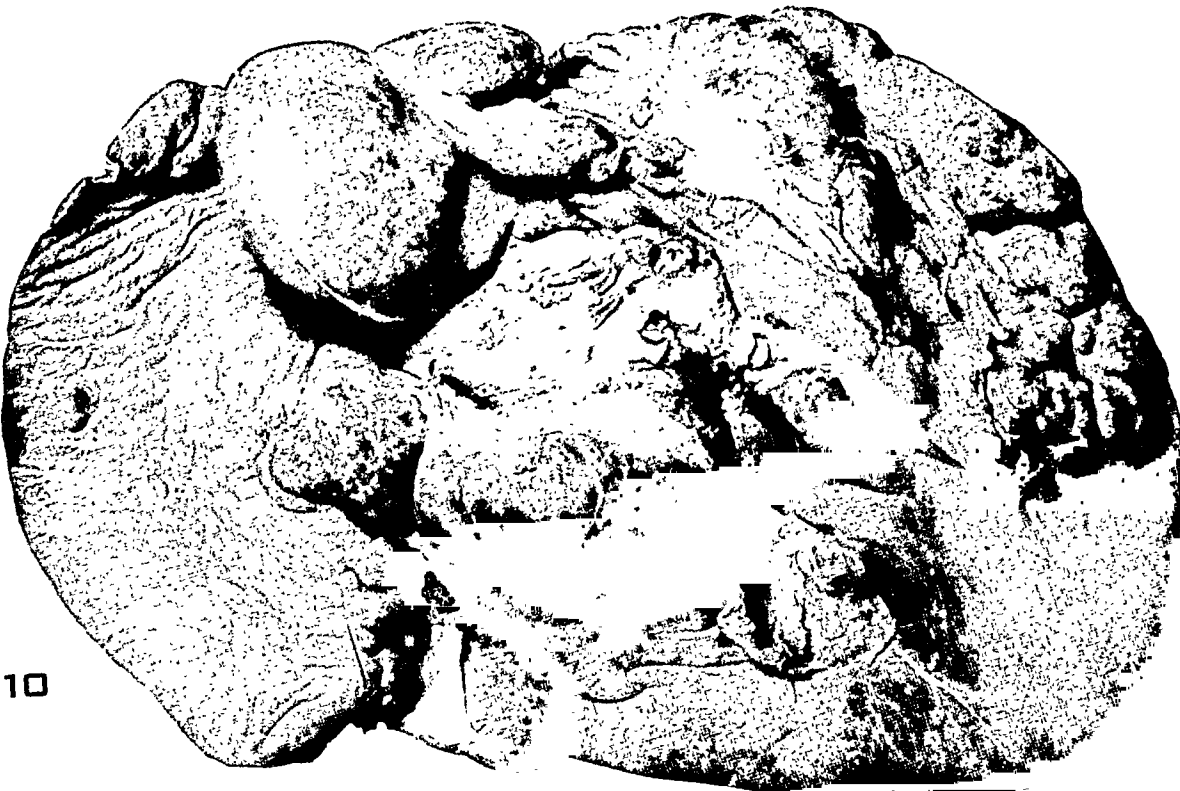
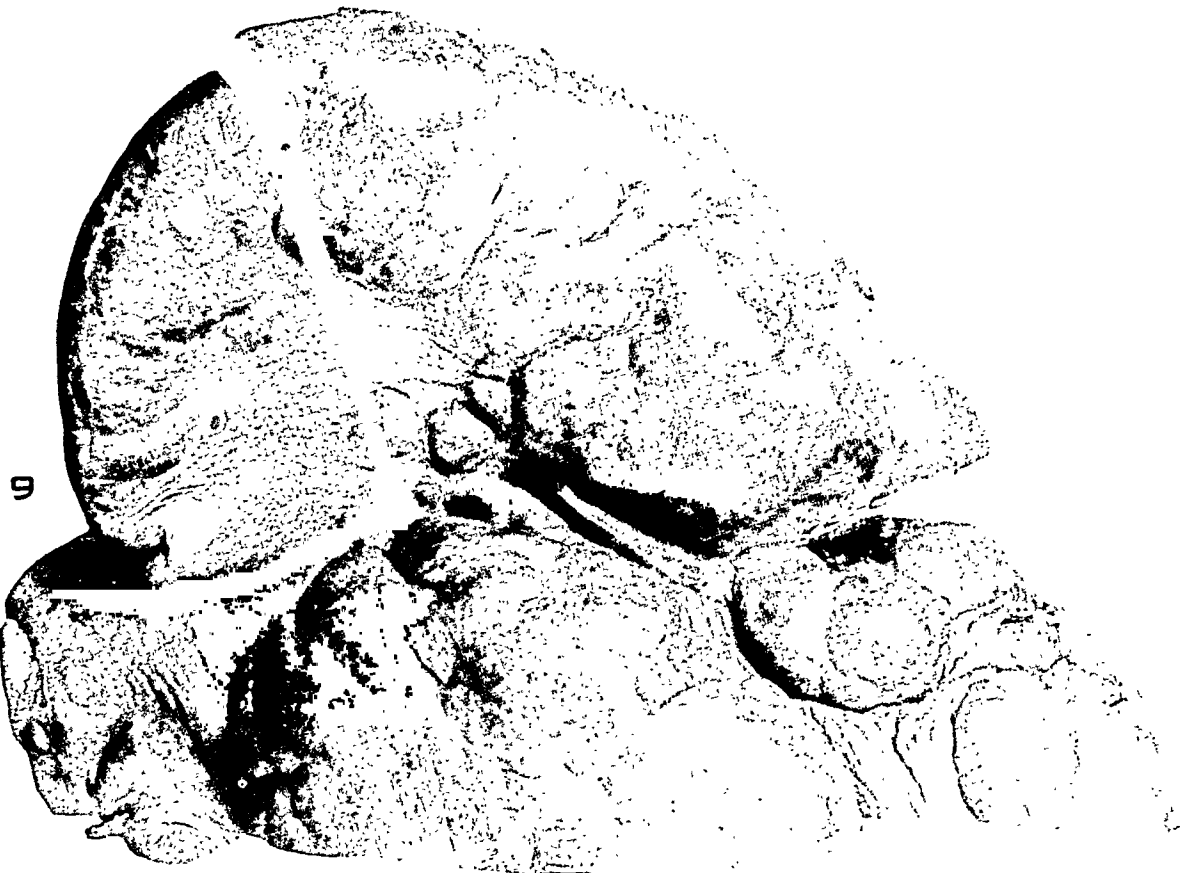


PLATE 92

FIG. 9. Case 92. Duration of hepatitis, 69 days. Weight of liver, 1040 gm. Massive tumor-like areas of hyperplastic regenerated tissue project above sunken patches. The surface of sunken regions has the appearance of coarse-grained leather.

FIG. 10. Case 124. Duration of disease, 37 days. Weight of liver, 800 gm. Under surface of organ shows numerous coarse nodules; the remainder has a smooth or finely wrinkled appearance. (See Figs. 73 and 75 for changes in the brain of this case.)



0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

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Pathology of Fatal Epidemic Hepatitis

PLATE 93

FIG. 11. Case 84. Duration of disease, 93 days. Weight of liver, 1710 gm. The cut surface shows extensive pale areas of regenerated "lobules"; between them lie depressed patches of tissue having a smooth texture and a fleshy appearance. (The microscopic structure of a regenerated "lobule" is shown in Figs. 5, 32, 37 and 46. For structure of the kidney of this case see Figs. 60 and 61; for brain changes see Figs. 71 and 72.)

FIG. 12. Case 76. Duration of disease, 96 days. Weight of liver, 2100 gm. This is an example of massive regenerative hyperplasia limited almost exclusively to the right lobe; the left lobe consists chiefly of collapsed stroma. (See Fig. 20 for appearance of reticulum in left lobe, and Figs. 67, 68, 69 and 76 for changes in the brain.)



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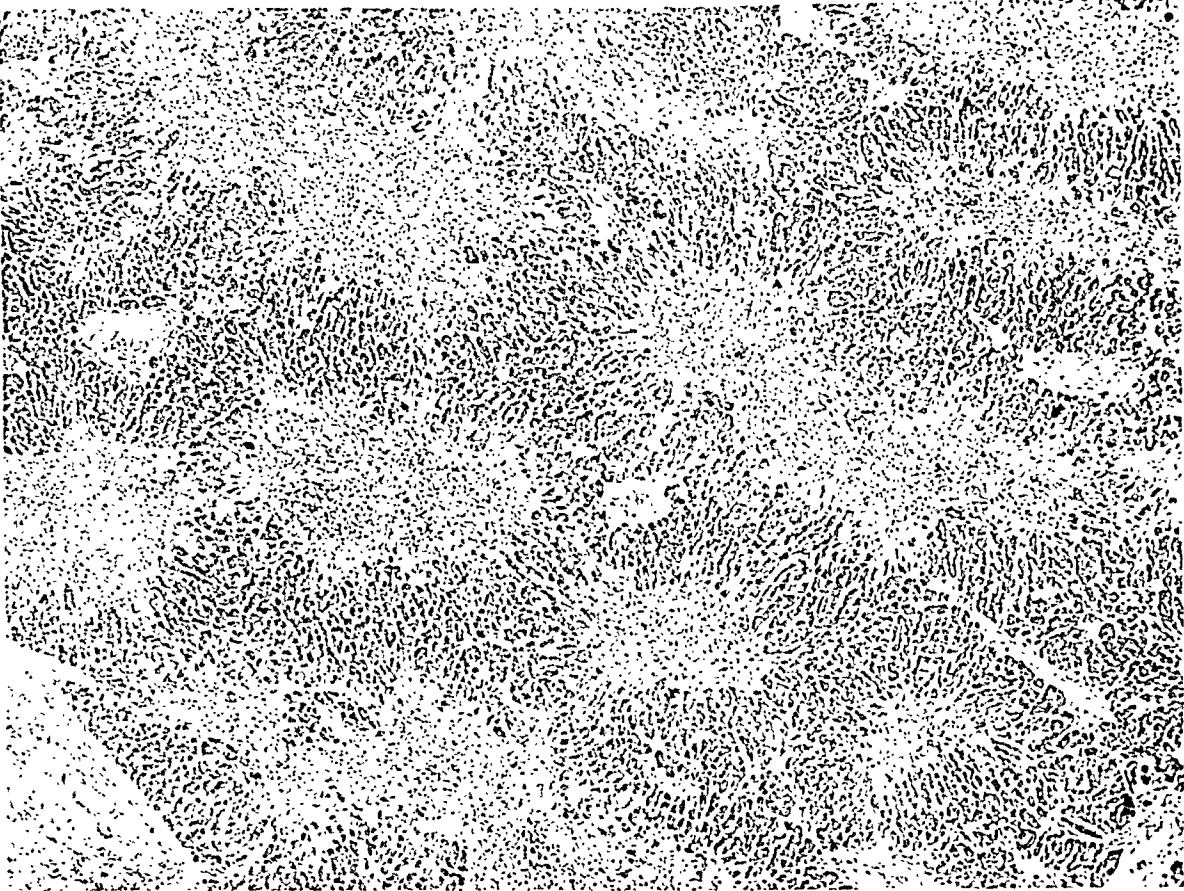
Pathology of Fatal Epidemic Hepatitis

PLATE 94

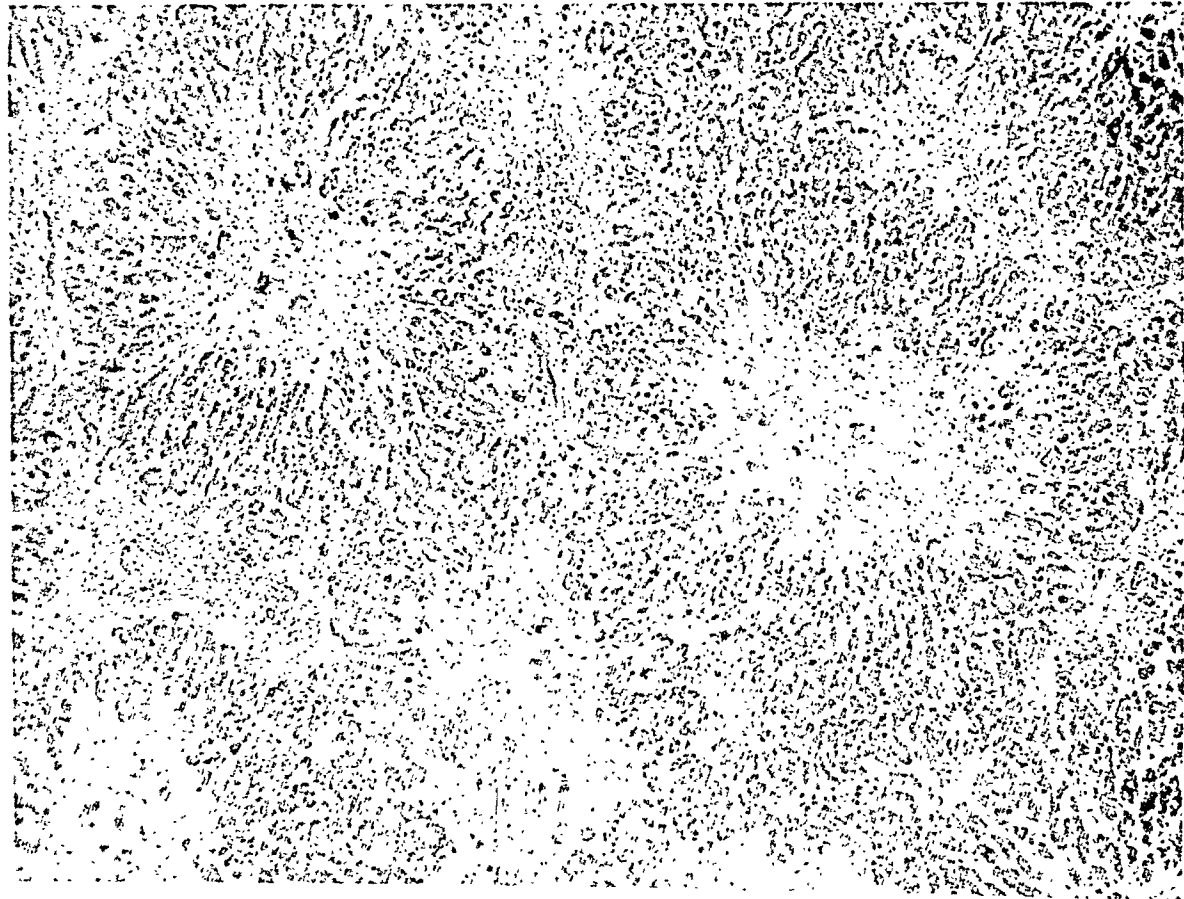
FIG. 13. Case 4. Duration of disease, 10 days. The central parts of the lobules have been destroyed; the peripheral rim of hepatic cells has remained more or less intact. (See Fig. 16 for details of cellular reaction within the stroma of the central portion of the lobules, Fig. 21 for changes in an efferent vein. Figs. 24, 25 and 26 for early regenerative activity, and Fig. 39 for appearance of portal canals and interlobular bile ducts.) $\times 35$.

FIG. 14. Case 18. Duration of hepatitis, 30 days. The central zones of the lobules are largely destroyed, leaving a peripheral rim of parenchyma. $\times 120$.

3



14



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Pathology of Fatal Epidemic Hepatitis

PLATE 95

FIG. 15. Case 15. Duration of hepatitis, 14 days. The figure shows extensive destruction of parenchyma leaving only isolated broken columns of cells at the periphery of some lobules. The stroma is infiltrated with macrophages and exudative cells. (See Fig. 40 for appearance of interlobular and septal bile ducts.) $\times 135$.

FIG. 16. Case 4. Duration of disease, 10 days. The photomicrograph shows the central part of a lobule, the stroma of which is infiltrated with polymorphonuclear leukocytes, lymphocytes, plasma cells and pigmented macrophages. This pigment is lipofuscin. A clump of multinucleated liver cells is evidence of early regenerative activity. (See Fig. 24.) $\times 810$.

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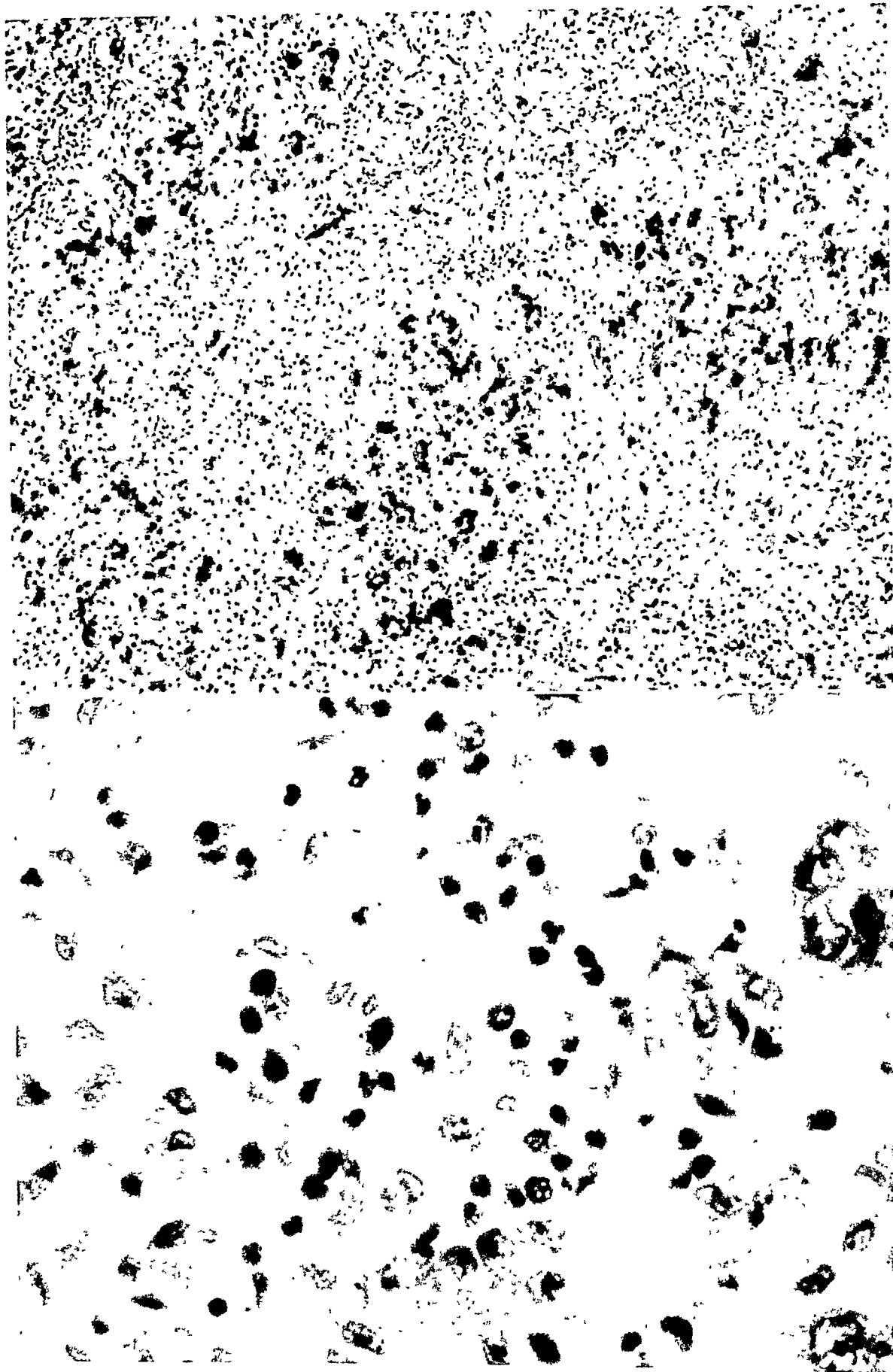
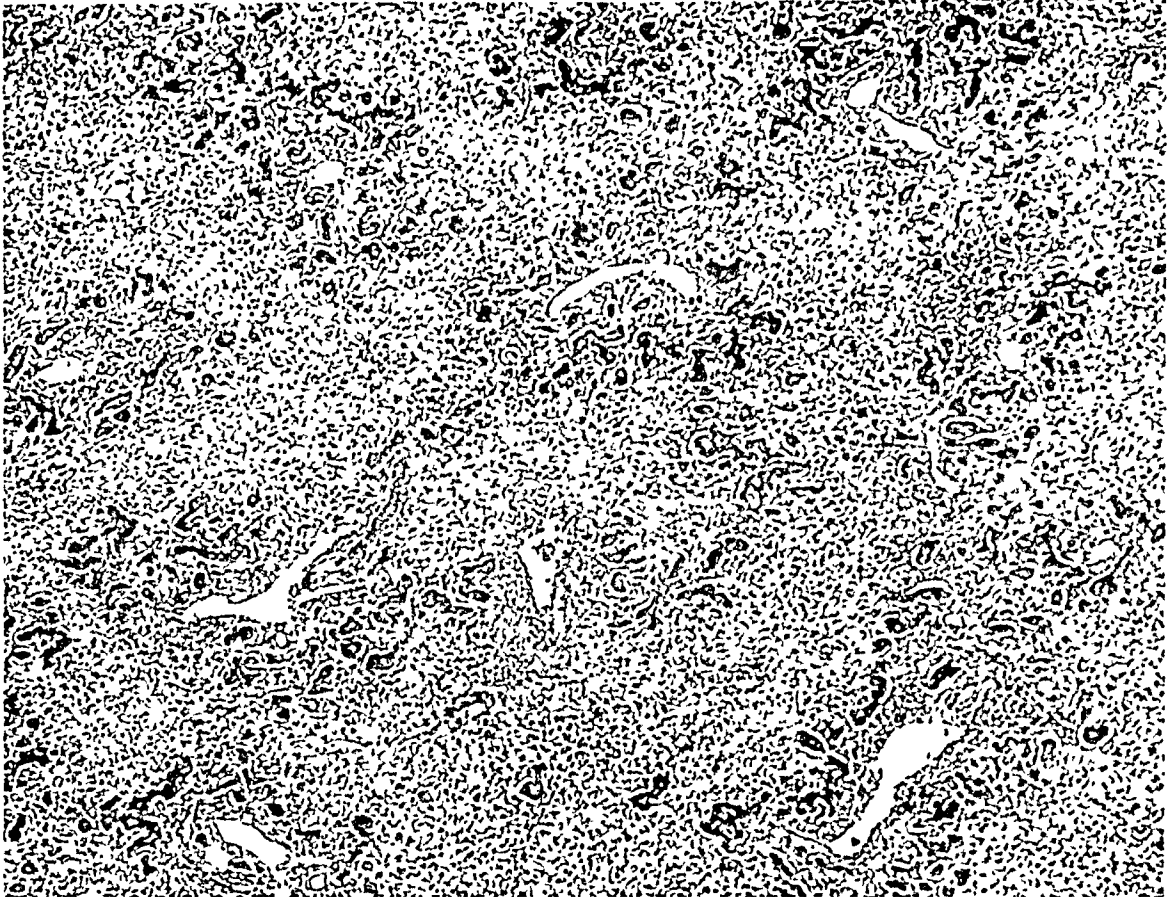


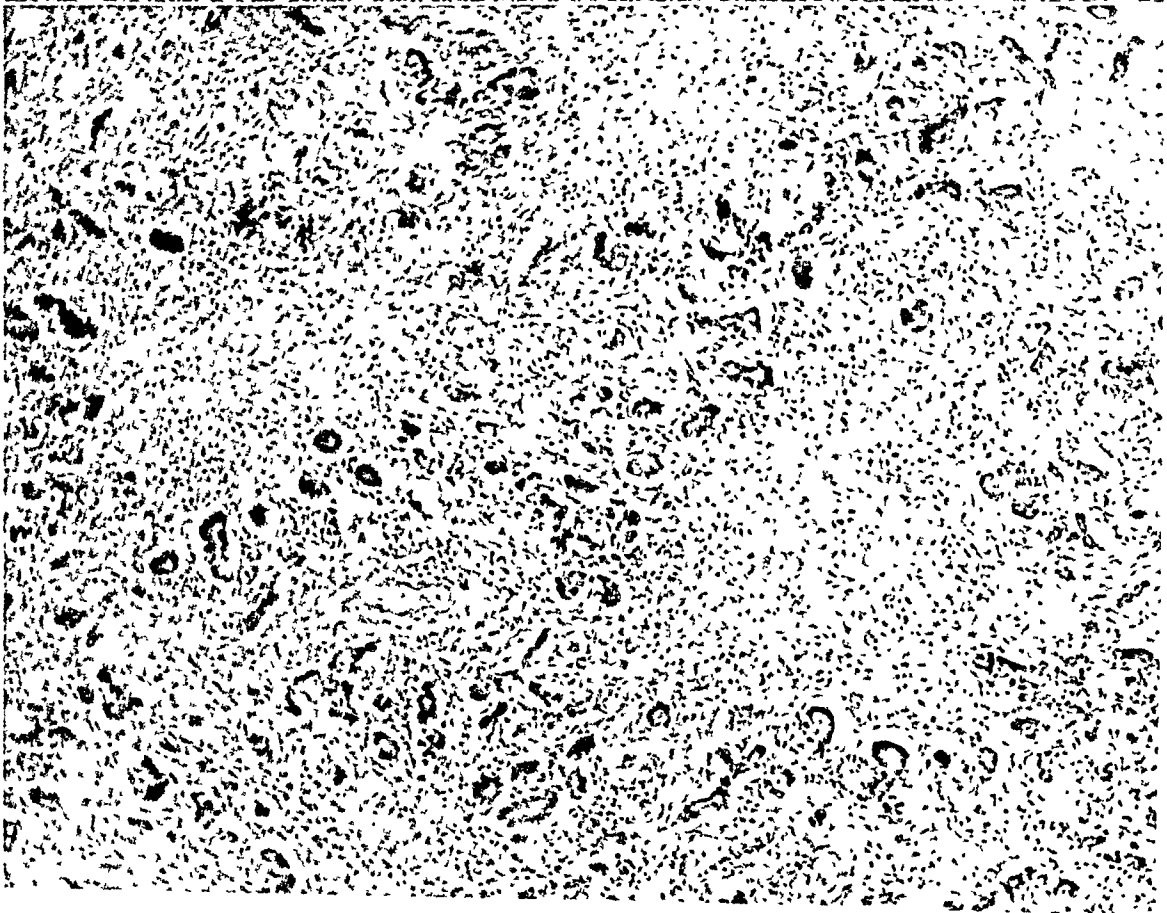
PLATE 96

- FIG. 17. Case 79. Duration of hepatitis, 57 days. The section is from an area of "red atrophy." The periphery of the lobular remnants is more or less outlined by stockades of branching bile ducts. (The condition of efferent veins from this case is shown in Figs. 22 and 23.) $\times 35$.
- FIG. 18. Case 93. Duration of disease, 76 days. From an area of "red atrophy." The outlines of lobular remnants are indicated by numerous small proliferating biliary ducts. (Elsewhere the liver from this case showed atypical regeneration of parenchyma; Fig. 34.) $\times 85$.

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Pathology of Fatal Epidemic Hepatitis

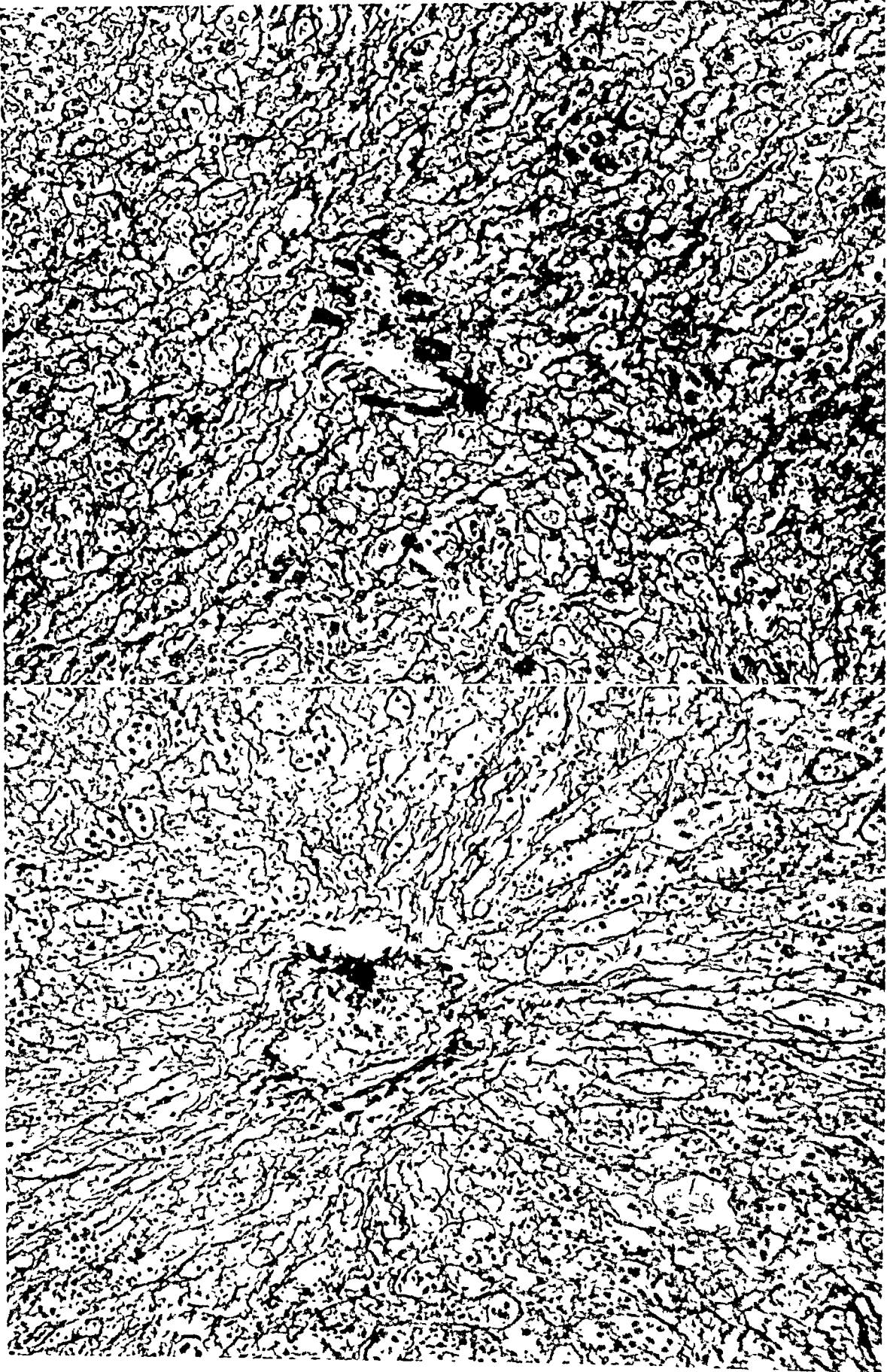
PLATE 97

FIG. 19. Case 80. Duration of hepatitis, 30 days. The interlobar stroma from an area of "red atrophy" has remained intact. Because of loss of liver cells the meshes of the reticulum framework are narrowed and partly collapsed. Wilder's reticulum stain. (Branching bile ducts from this case are shown in Fig. 41; a photomicrograph of the spleen, in Fig. 57.) $\times 330$.

FIG. 20. Case 76. Duration of disease, 96 days. The lobular reticulum is intact and, in general, has a normal pattern, although its meshes are somewhat distorted. The section is taken from the atrophic left lobe of the liver shown in Figure 12. (For changes in the brain of this case see Figs. 67, 68, 69 and 76.) $\times 170$.

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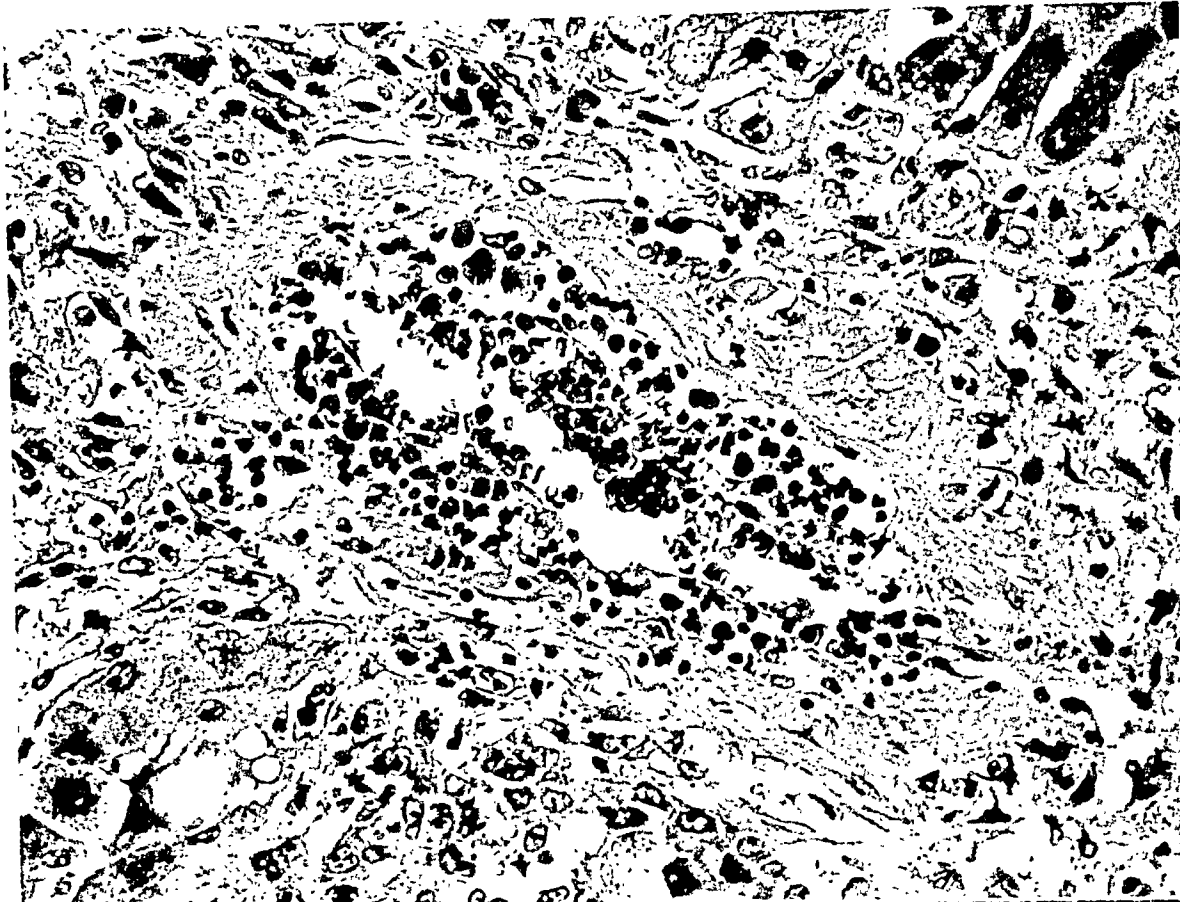
Pathology of Fatal Epidemic Hepatitis

PLATE 98

FIG. 21. Case 4. Duration of disease, 10 days. A central lobular vein has a greatly thickened wall which appears hyalinized. The subendothelial layer of the vein is infiltrated with cells of the same types as shown in Figure 16; the endothelial lining is intact. (See Figs. 13, 16, 24, 25, 26 and 39 for other photomicrographs of liver from same case.) $\times 500$.

FIG. 22. Case 79. Duration of hepatitis, 57 days. A sublobular vein shows marked endophlebitis. (See Fig. 17 for appearance of the surrounding tissues.) $\times 175$.

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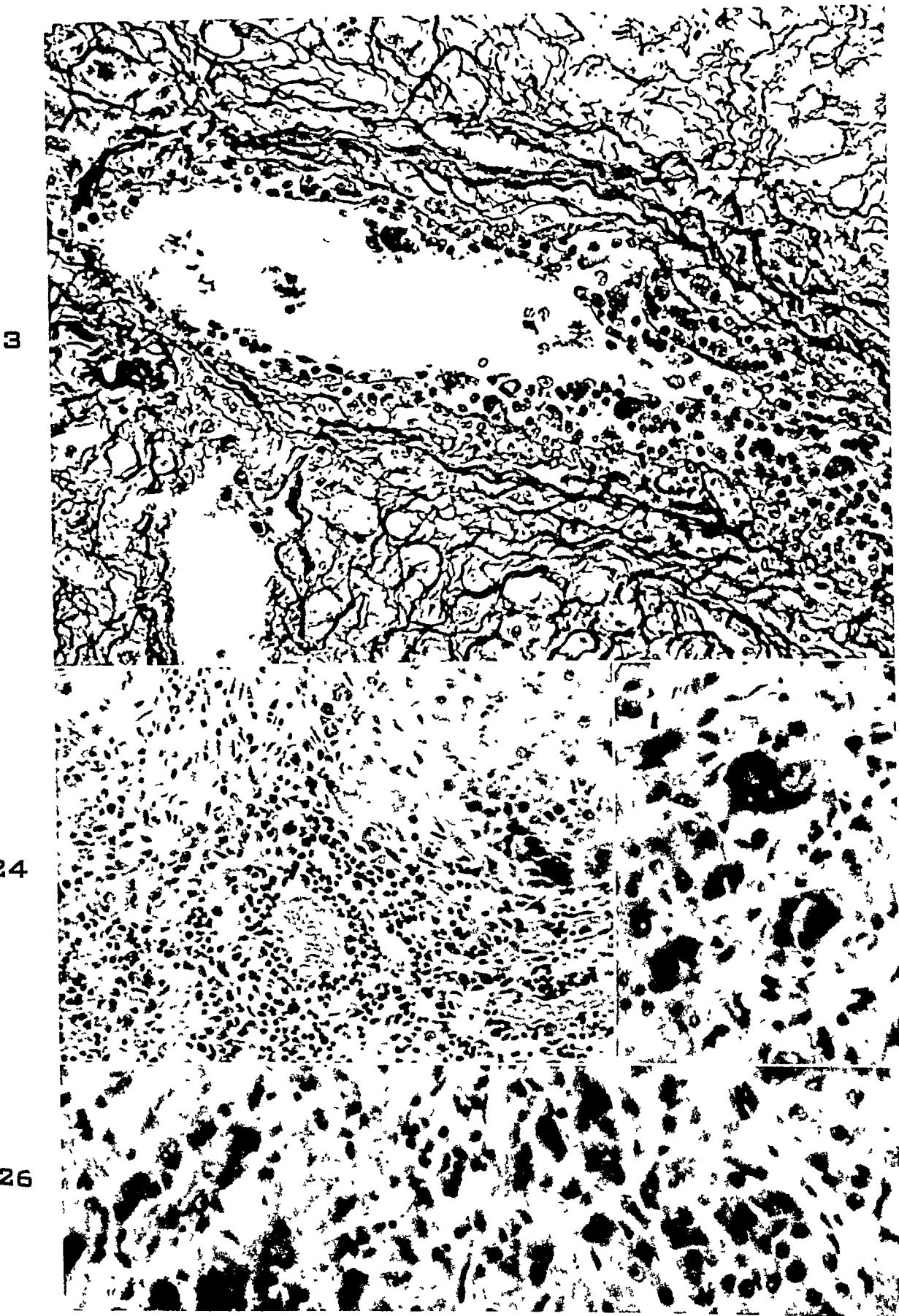


22



PLATE 99

- FIG. 23. Case 79. Duration of disease, 57 days. A sublobular vein stained by Wilder's reticulum stain shows that the endothelium of the intima is intact. The subendothelial layer is infiltrated with numerous cells, some of which are pigmented macrophages. The walls of the vein have a loose structure. $\times 500$.
- FIG. 24. Case 4. Duration of disease, 10 days. Early multiplication of liver cells is shown adjacent to a region from which the parenchyma has disappeared. The regenerating cells have closely aggregated, deeply staining large nuclei. The stroma of the central part of the lobule is infiltrated with wandering cells, details of which are shown in Figure 16. The central lobular vein exhibits marked endophlebitis. (See Fig. 21 for details.) $\times 110$.
- FIG. 25. Case 4. Duration of disease, 10 days. The partly broken columns of liver cells show early regeneration, as indicated by numerous closely placed hyperchromatic nuclei; many cells are binucleated. $\times 330$.
- FIG. 26. Another field from the section shown in Figure 25. $\times 330$.



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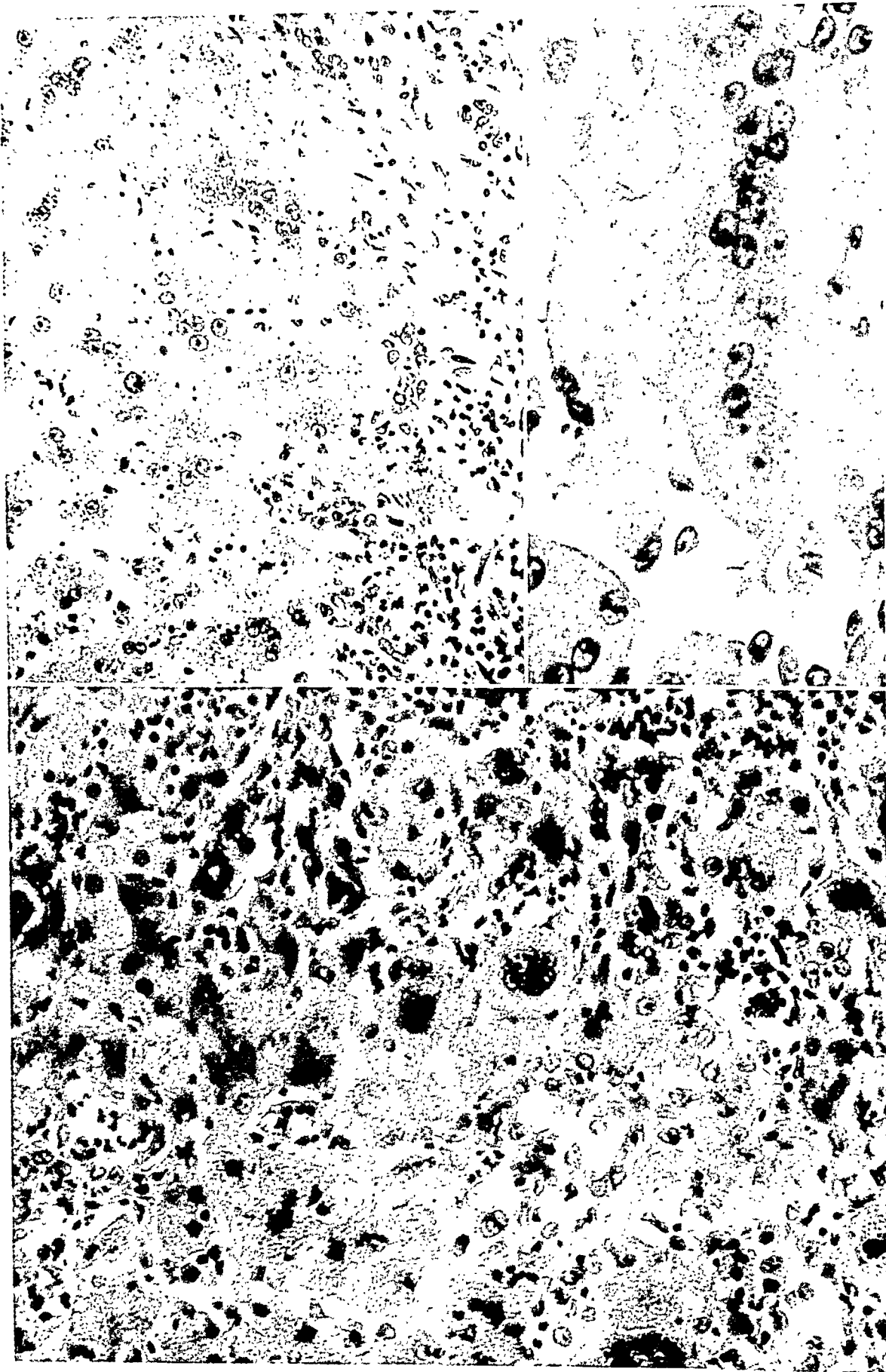
Pathology of Fatal Epidemic Hepatitis

PLATE 100

FIG. 27. Case 8. Duration of disease, 43 days. A large multinucleated liver cell from an area of regeneration. The section is taken from the nodular areas of regeneration shown grossly in Figure 3. $\times 300$.

FIG. 28. Case 8. Duration of disease, 43 days. A multinucleated liver "giant" cell at higher magnification than in Figure 27. The cytoplasm of the cell contains granules of bile pigment. $\times 700$.

FIG. 29. Case 53. Duration of disease, 34 days. A group of liver cells, which are arranged in such a disorderly manner as to simulate neoplasia. A number of cells are multinucleated. The cytoplasm of most cells has a granular appearance because of the presence of bile. $\times 200$.



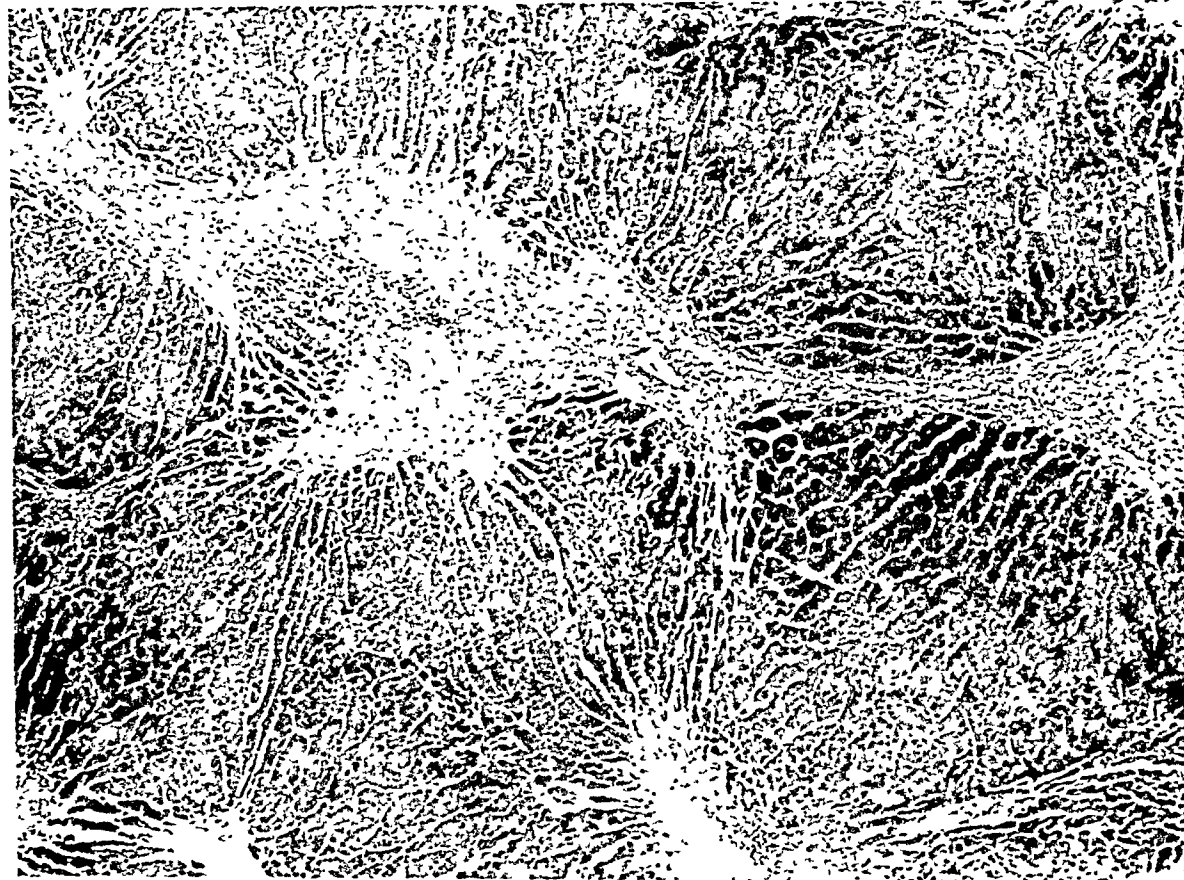
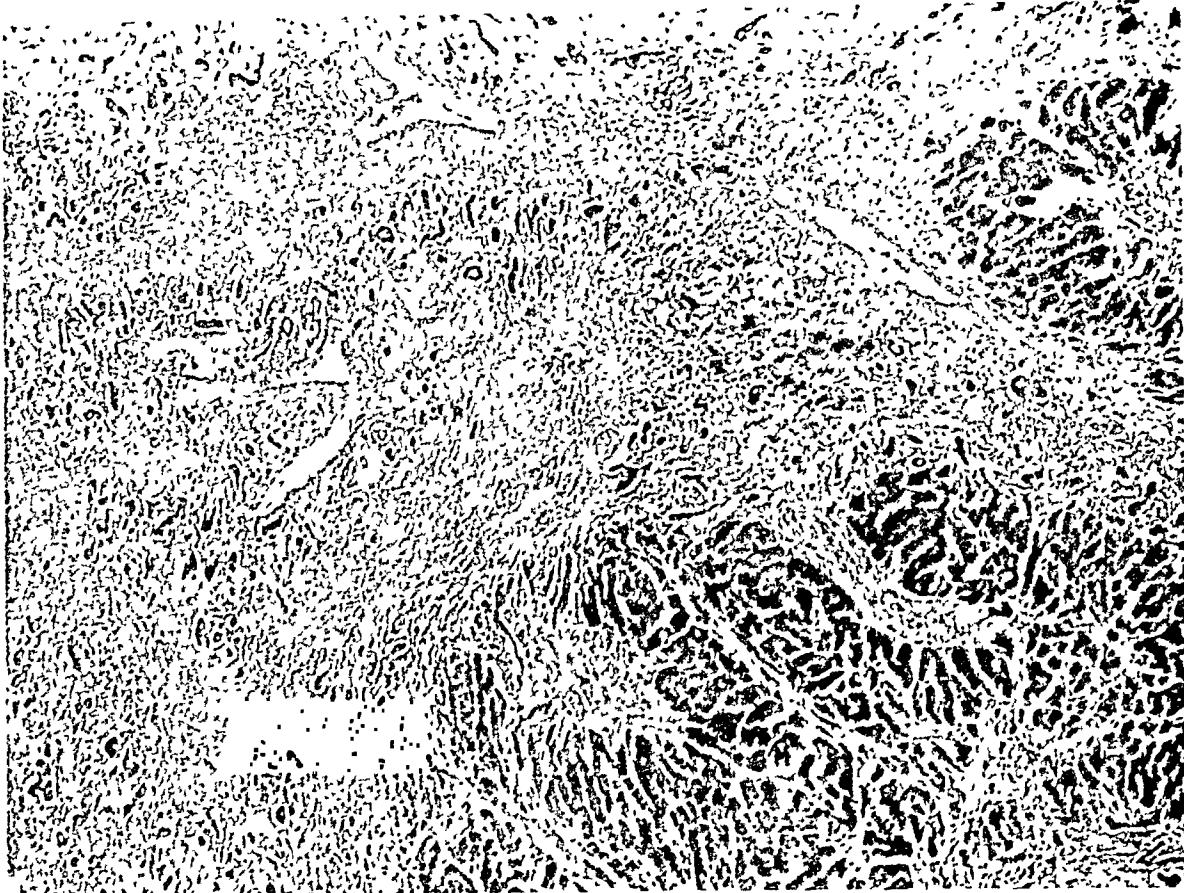
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Pathology of Fatal Epidemic Hepatitis

PLATE 101

FIG. 30. Case 24. Duration of disease, 26 days. The photomicrograph shows the edge of a region of regenerative hyperplasia. The section was taken from the liver illustrated in Figure 1. The hyperplastic parenchyma has no orderly arrangement. Where complete destruction has occurred, the lobular outlines are still indicated by proliferating bile ducts. The empty stroma stains darkly because of excessive blood in the sinusoids. $\times 35$.

FIG. 31. Case 81. Duration of disease, 19 days. The section has been taken from one of the yellow patches of regenerating "lobules" shown in Figure 2. The newly formed "lobules" are large, have an atypical structure and are noticeably ischemic. (Fig. 4 shows the microscopic appearance of the liver from this case in the regions of "red atrophy"; here the sinusoids are prominently distended.) $\times 50$.



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Pathology of Fatal Epidemic Hepatitis

PLATE 102

- FIG. 32. Case 84. Duration of disease, 93 days. Section from nodular areas shown grossly in Figure 11. Large, confluent patches of parenchyma are seen; there is no arrangement into definite lobules. (See Figs. 37 and 46 for higher magnification; the changes in the kidney from this case are shown in Figs. 60 and 61; the brain changes in Figs. 71 and 72.) $\times 35$.
- FIG. 33. Case 86. Duration of disease, 62 days. The reticulum framework and the columns of liver cells converge in normal manner toward the central lobular vein. (See Fig. 70 for changes in the brain.) $\times 200$.

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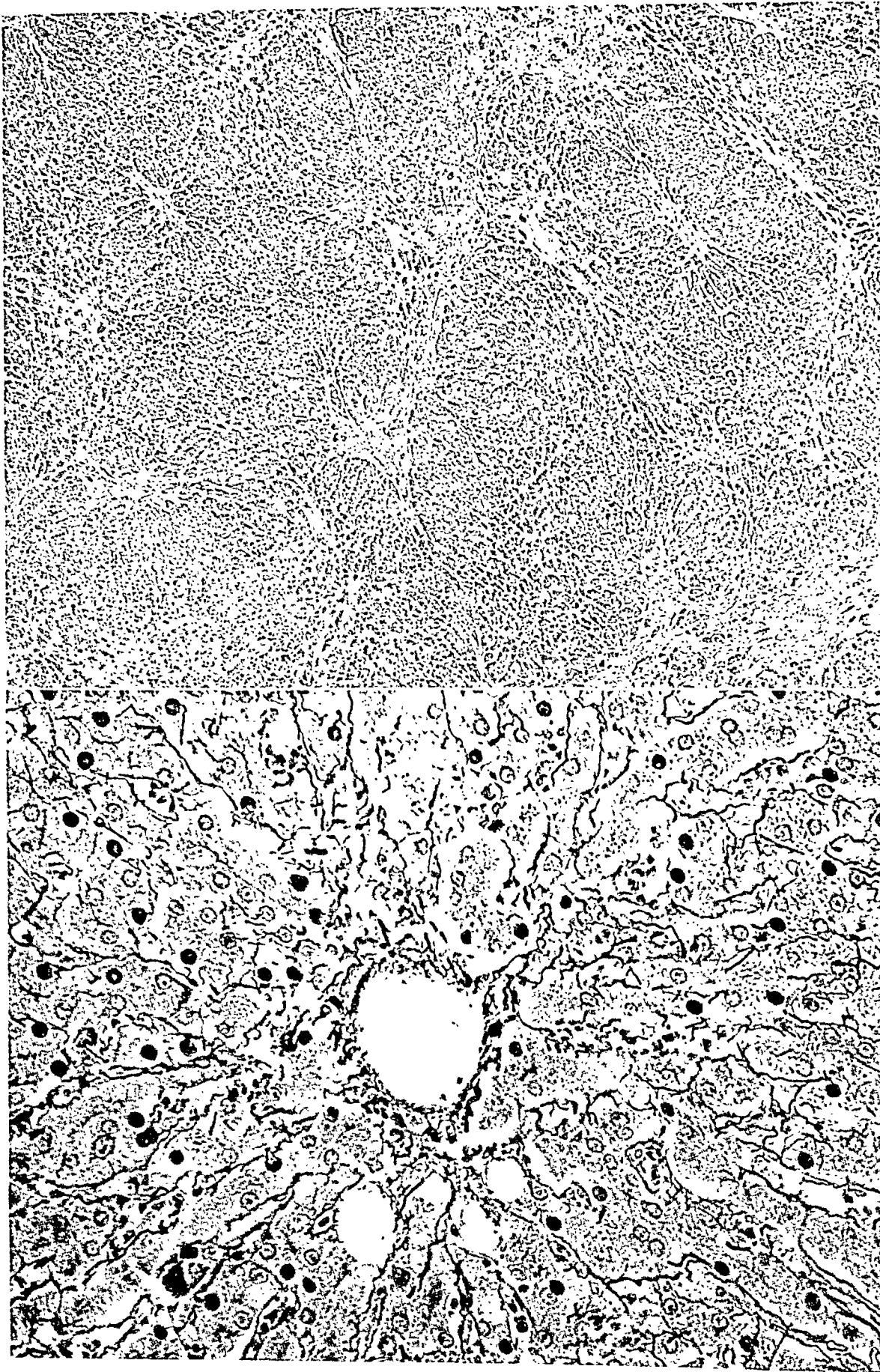
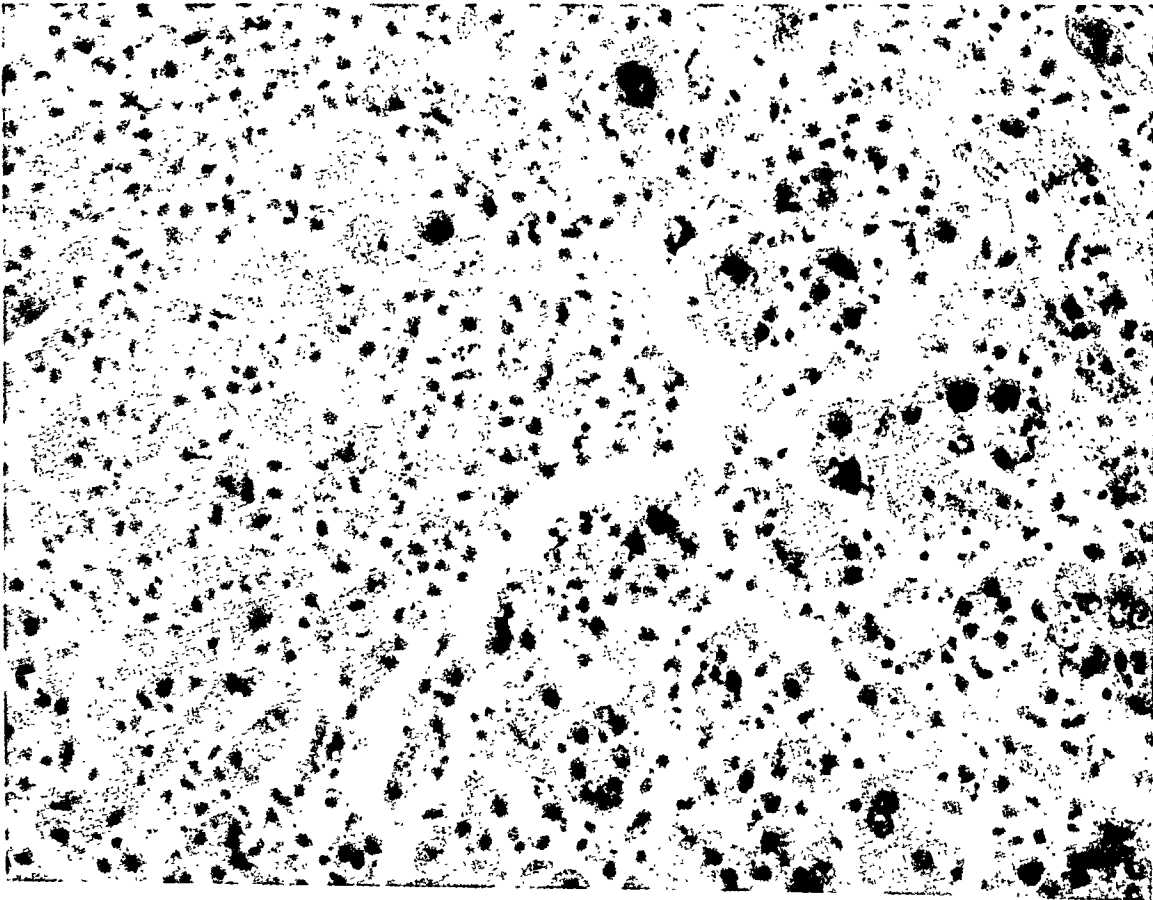


PLATE 103

FIG. 34. Case 93. Duration of disease, 76 days. A large hyperplastic "lobule," the central region of which is made up of atrophic and more or less disunited liver cells, whereas the cells at the periphery form columns. (Fig. 18, from the same case, shows a region of complete destruction of hepatic parenchyma, with preservation of the bile ducts.) $\times 60$.

FIG. 35. Case 58. Duration of disease, 40 days. Secondary degeneration in an area of regenerative hyperplasia. Because of marked ischemia and perhaps other factors, the newly formed cells are undergoing degenerative changes. (The large size and hyperchromatic nuclei of the hyperplastic liver cells are noteworthy features.) A marked lymphocytic and polymorphonuclear reaction is seen in the stroma. $\times 200$.



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Pathology of Fatal Epidemic Hepatitis

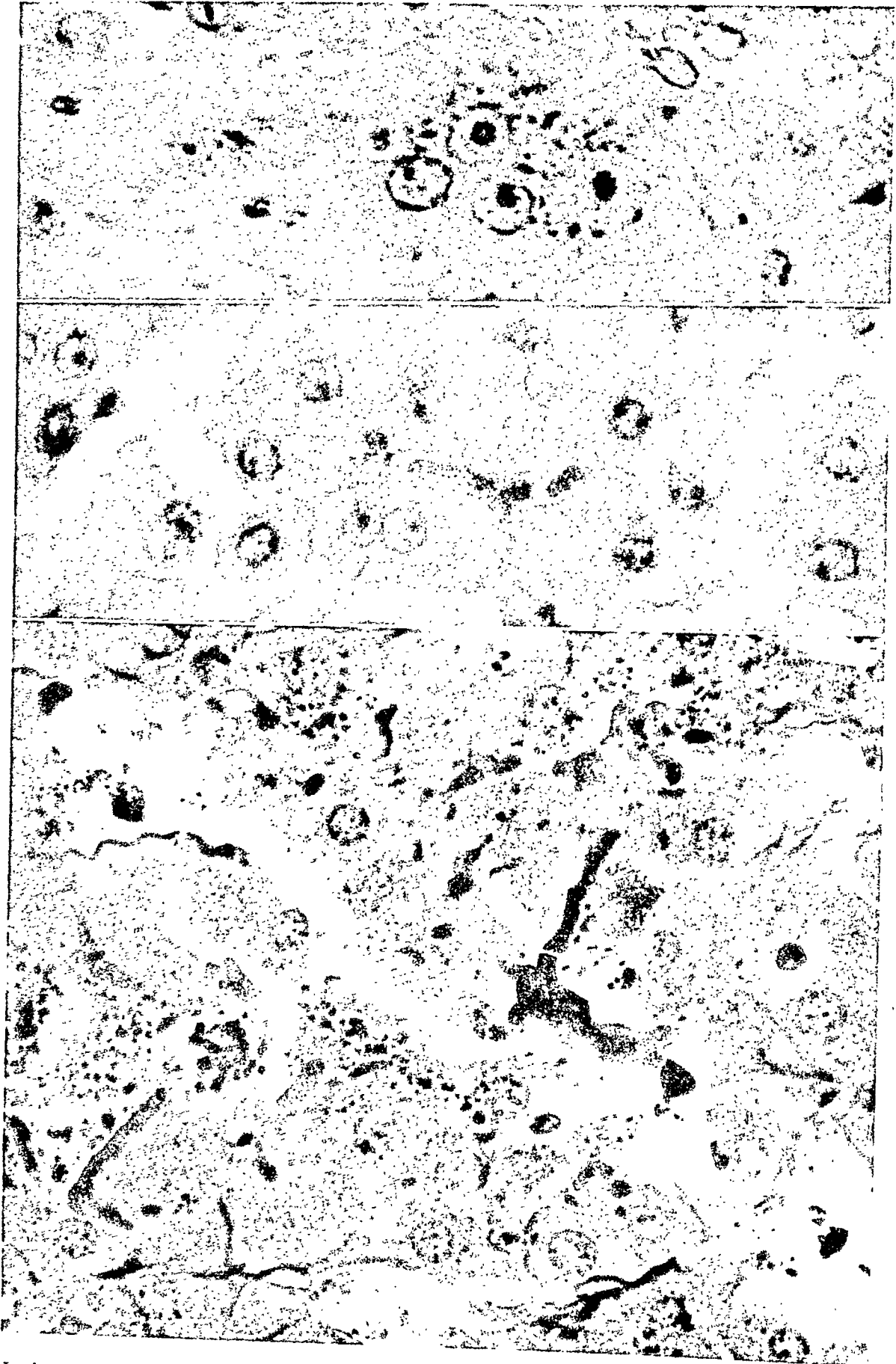
PLATE 104

- FIG. 36. Case 66. Duration of disease, 24 days. A multinucleated "giant" liver cell, the nuclei of which have prominent nucleoli. The latter must not be mistaken for intranuclear inclusion bodies. $\times 1000$.
- FIG. 37. Case 84. Duration of disease, 93 days. The bile canaliculus of an hepatic column is distended with a plug of inspissated bile. The liver cells are well preserved. (The gross appearance of this liver is shown in Fig. 11; for general structural changes see Figs. 5, 32 and 46; for lesions in the kidney, Figs. 60 and 61, and for brain changes, Figs. 71 and 72.) $\times 1000$.
- FIG. 38. Case 117. Duration of disease, 240 days. Section is stained with Wilder's reticulum stain. Near the center of the figure is seen a thick branching bile "thrombus"; several other bile "thrombi" lie within the nearby canaliculi; the individual liver cells contain coarse granules of bile. $\times 850$.

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Lucké

Pathology of Fatal Epidemic Hepatitis

PLATE 105

- FIG. 39. Case 4. Duration of disease, 10 days. A portal triad with several large interlobular bile ducts having normal structure. The branches of the portal vein and hepatic artery likewise are normal. $\times 100$.
- FIG. 40. Case 15. Duration of disease, 14 days. Early budding of biliary ducts. The portal stroma is richly cellular. (Fig. 15 shows the extent of parenchymatous destruction in nearby parts of the liver of the same case.) $\times 125$.
- FIG. 41. Case 80. Duration of disease, 30 days. Proliferating bile duct at the periphery of a lobule. The lining cells have closely placed oval nuclei and scanty cytoplasm. $\times 350$.

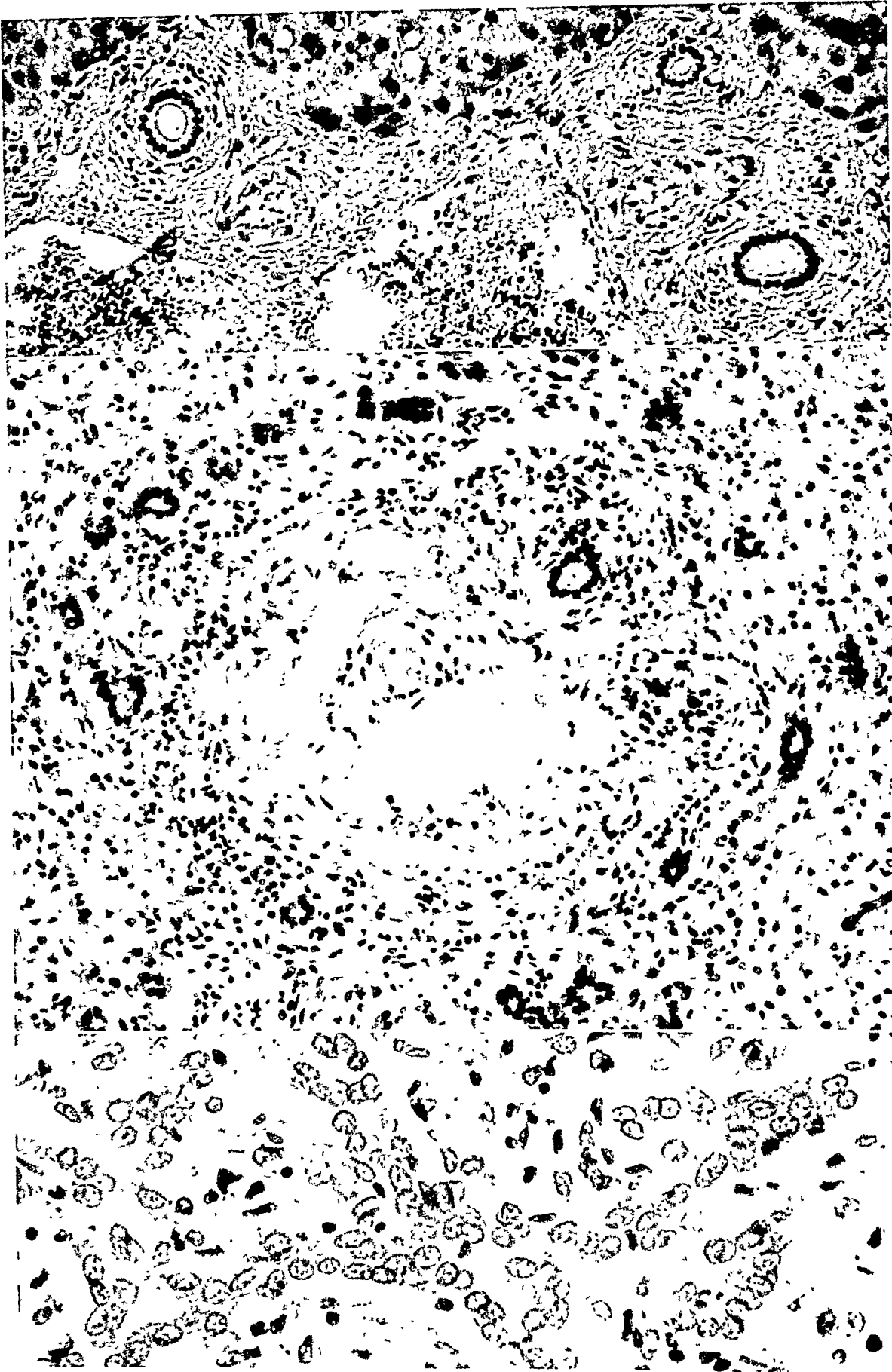
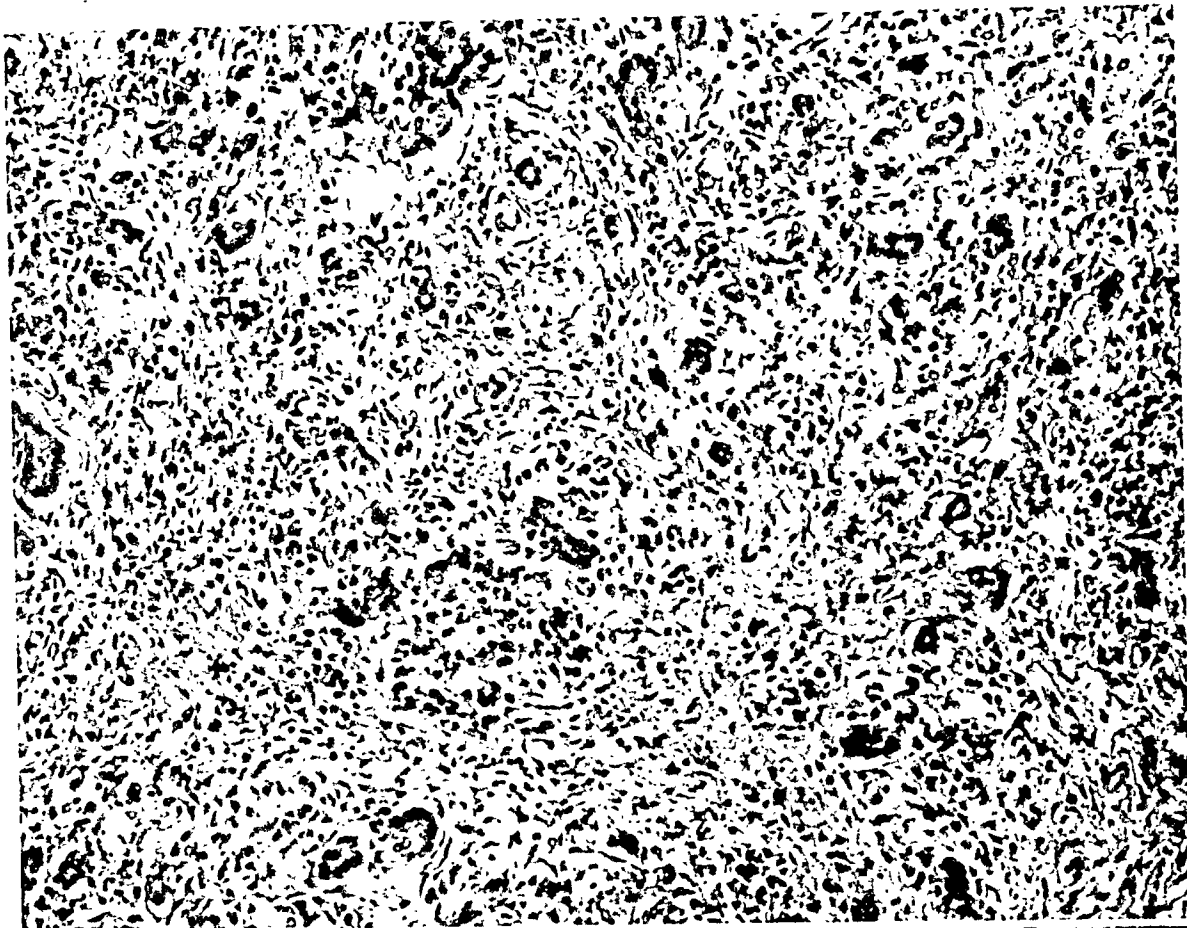


PLATE 106

- FIG. 42. Case 117. Duration of disease, 240 days. In regions in which the hepatic cells had been destroyed completely, proliferated small bile ducts remain in a richly vascular stroma. $\times 150$.
- FIG. 43. Case 46. Duration of disease, 15 days. Tubular structures at the periphery of a lobule; some parts of the tubules are lined by cells resembling bile duct epithelium, whereas other parts are lined by elements resembling liver cells. $\times 400$.

2



43

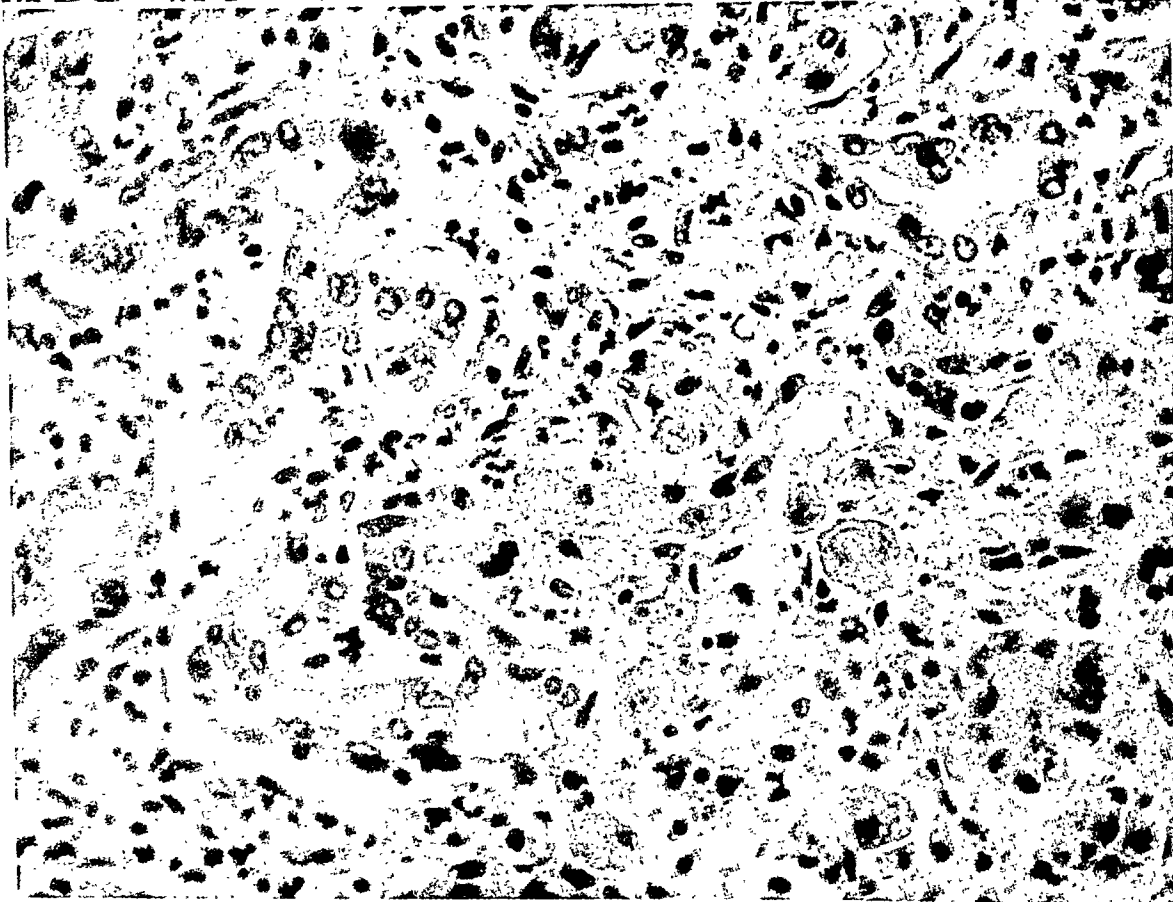
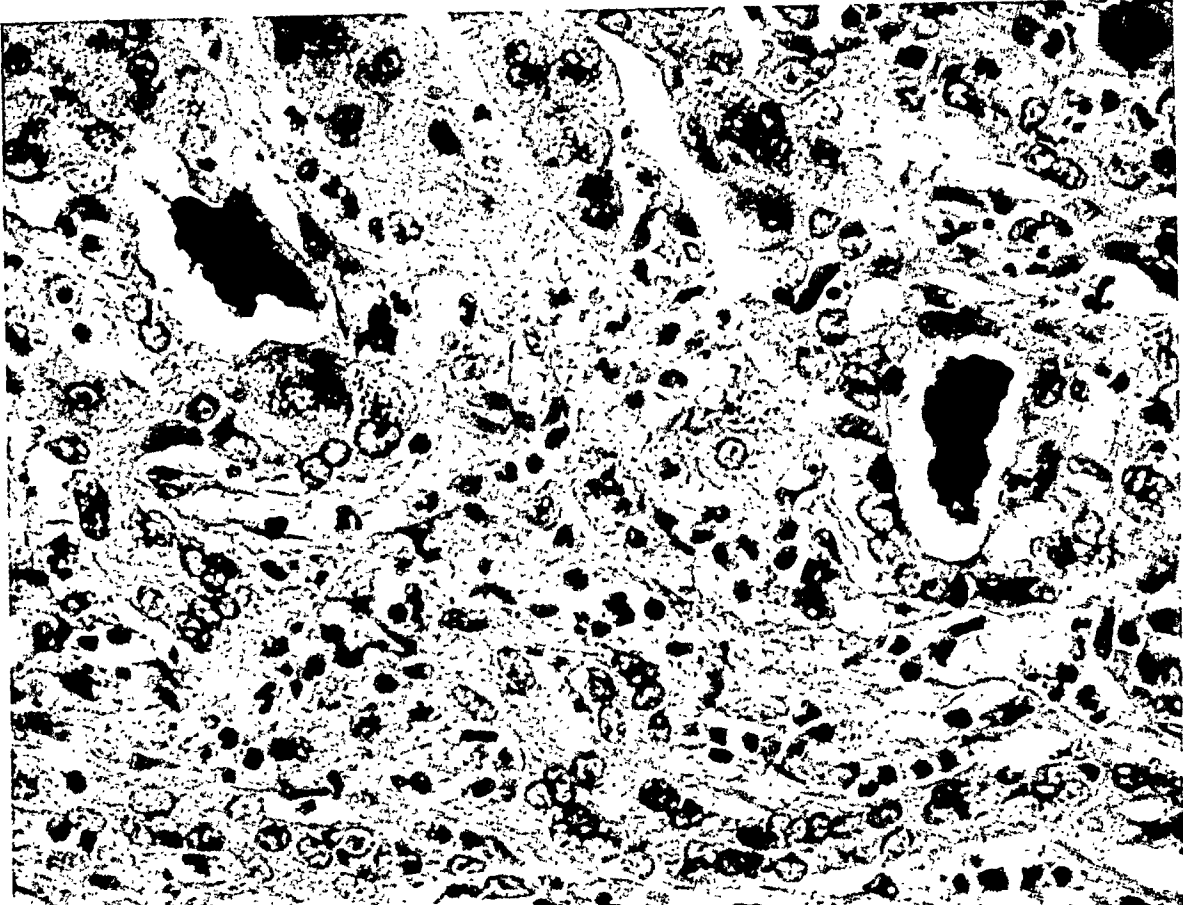


PLATE 107

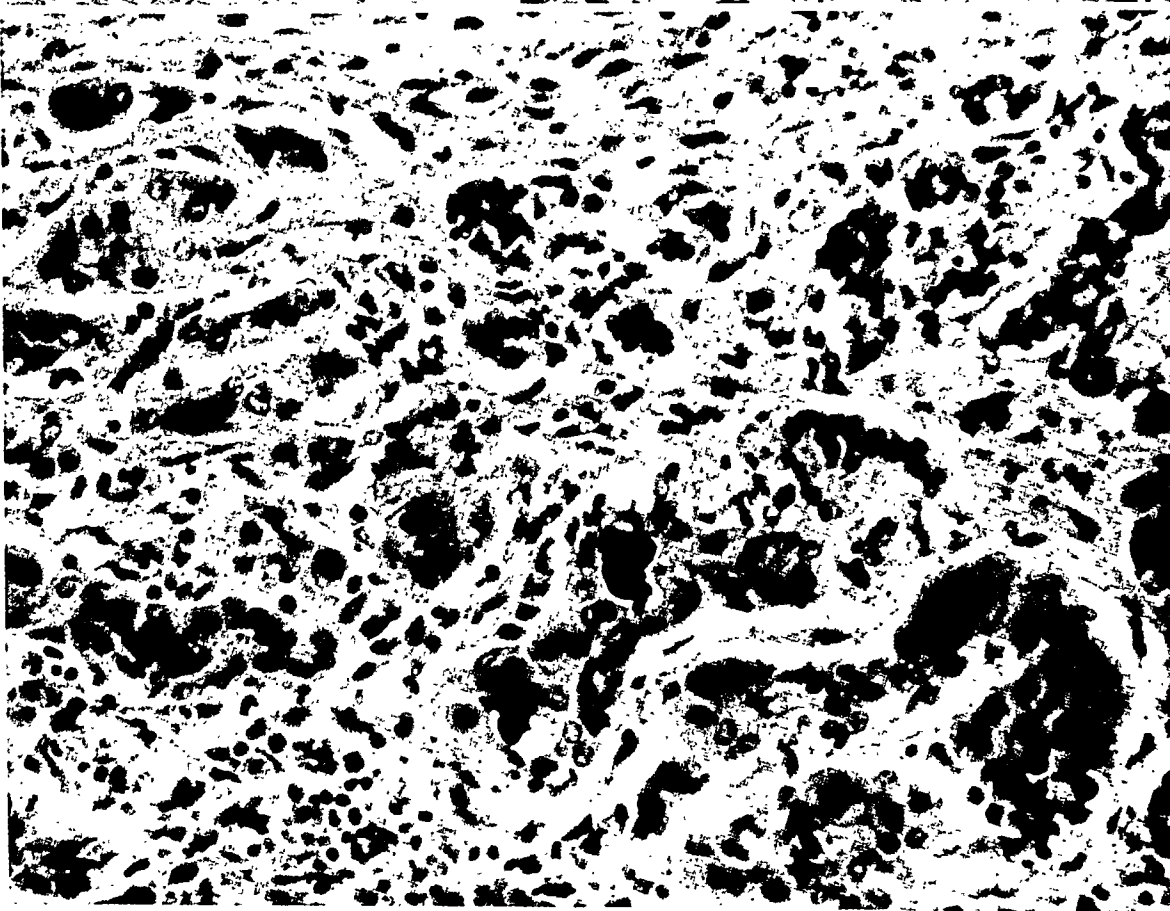
FIG. 44. Case 92. Duration of disease, 69 days. Two large clumps of bile, one lying in a widely dilated intracolumnar canaliculus, the other in a tubule apparently lined by biliary epithelium. (See Fig. 9 for gross appearance of liver, and Fig. 59 for changes in kidney.) $\times 550$.

FIG. 45. Case 113. Duration of disease, 154 days. The lumina of tubular structures at the periphery of lobular remnants contain clumps of bile. It is impossible to be sure whether these tubules are composed of biliary epithelium or of liver cells. $\times 350$.

4



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Pathology of Fatal Epidemic Hepatitis

PLATE 108

FIG. 46. Case 84. Duration of disease, 93 days. The cells of the regenerated tubules closely resemble liver cells. Whether these cells are derived from biliary epithelium or from pre-existing liver cells is debatable. (See also Figs. 5, 11, 32, 37, 60, 61, 71 and 72 for photographs of other lesions in this case.) $\times 550$.

FIG. 47. Case 104. Duration of disease, 98 days. A cluster of tubules lined by liver cells lies at the periphery of a lobule. The location and appearance of the tubules suggest that they have been derived from bile ducts. (See also Fig. 7 from the same case which shows a branching bile duct connected with regenerated columns of liver cells.) $\times 300$.

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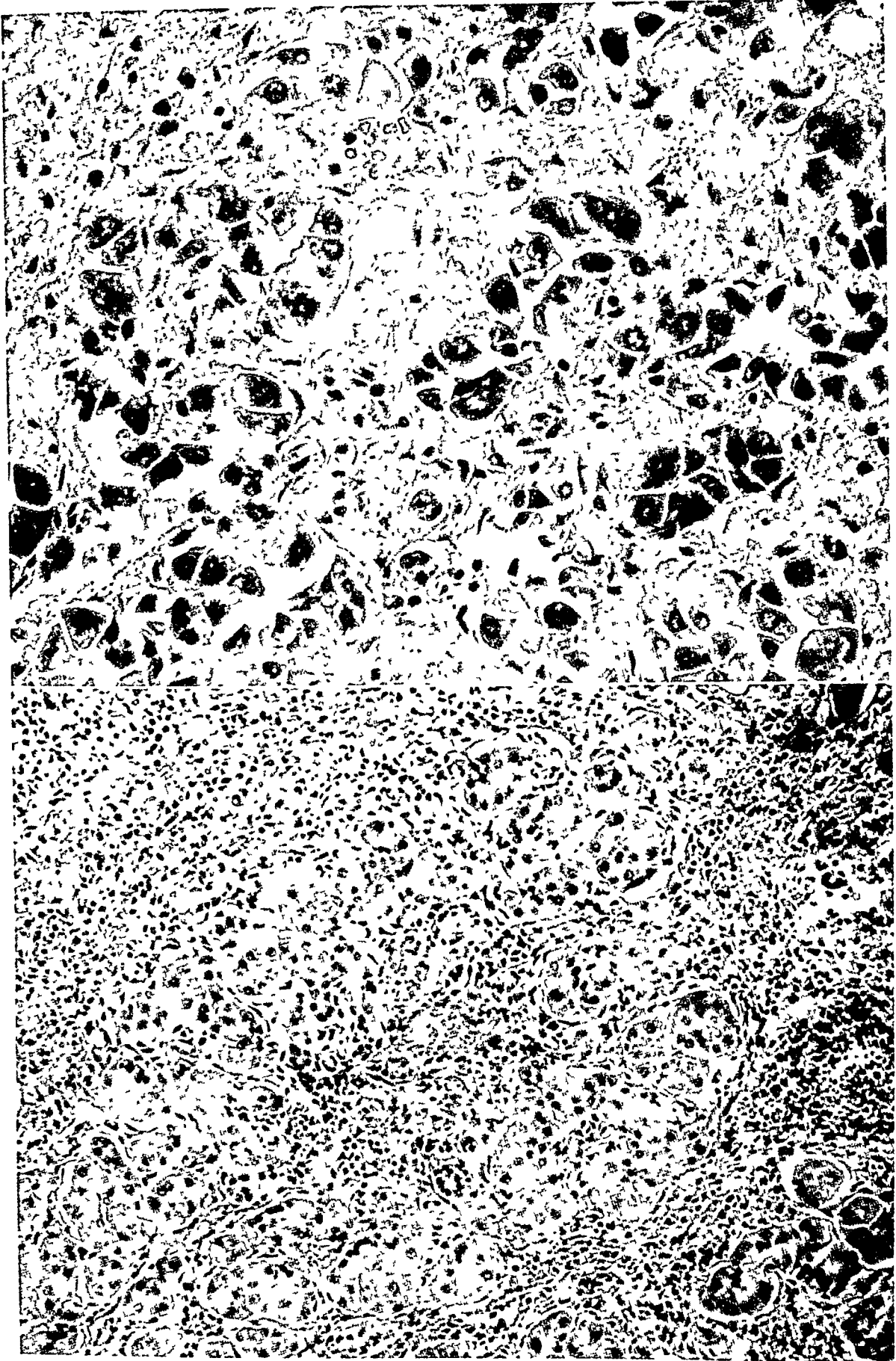


PLATE 109

FIG. 48. Case 22. Duration of hepatitis, 17 days. Cecum. The tissue is extremely edematous; the mucosa is thrown into thick folds. (See Fig. 51 for microscopic appearance.)

FIG. 49. Case 11. Duration of hepatitis, 64 days. Transverse sections of lower ileum showing edematous thickening of wall and of mesenteric attachment.

8



49



1 3 4 5 6 7 8 9

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Pathology of Fatal Epidemic Hepatitis

PLATE 110

FIG. 50. Case 43. Duration of hepatitis, 20 days. Low-power view of colon to show marked inflammatory edema of submucosa. The mucosa is intact. (See Fig. 52 for details of cellular reaction.) $\times 10$.

FIG. 51. Case 22. Duration of disease, 17 days. Low-power view of cecum shown in Figure 48. There is marked phlegmonous inflammation which is especially pronounced in the submucosa. The mucosa is preserved. $\times 10$.

0



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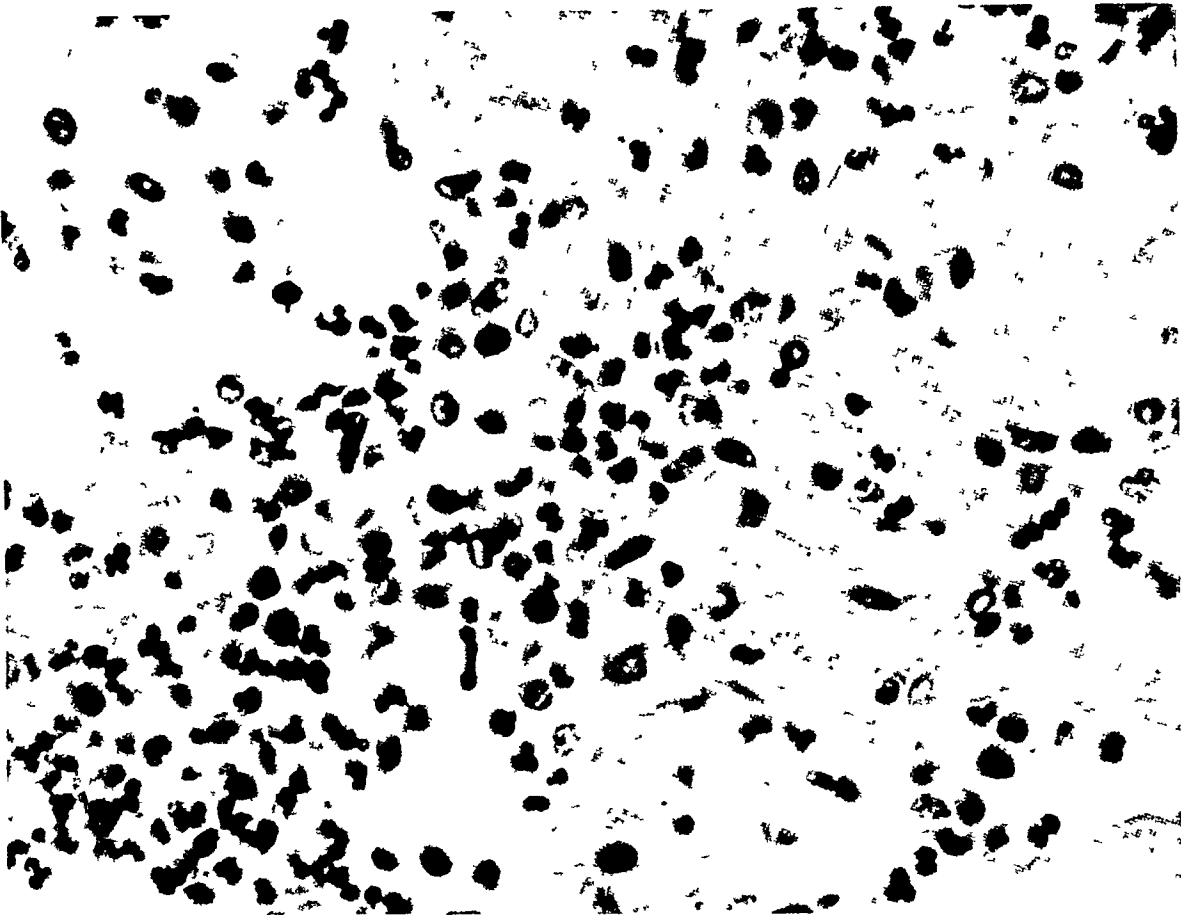


Pathology of Fatal Epidemic Hepatitis

PLATE III

- FIG. 52. Case 43. Duration of hepatitis, 20 days. Details of inflammatory edema of wall of cecum shown in Figure 50. The tissue is widely distended and everywhere invaded by polymorphonuclear leukocytes and macrophages. $\times 550$.
- FIG. 53. Case 94. Duration of hepatitis, 50 days. A low-power view of ileum showing marked distention of submucosa by edema. No inflammatory reaction is present. The mucosa is preserved. $\times 12$.

2



53



PLATE 112

FIG. 54. Case 8. Duration of hepatitis, 43 days. Ulceration of lower portion of esophagus with inflammatory reaction extending into deeper layers. (A gross photograph of the liver from this case is shown in Fig. 3, and the microscopic appearance of the liver in Figs. 27 and 28.) $\times 75$.

FIG. 55. Case 39. Duration of hepatitis, 34 days. Gallbladder showing marked edema and hemorrhages in mucosa. $\times 25$.

4

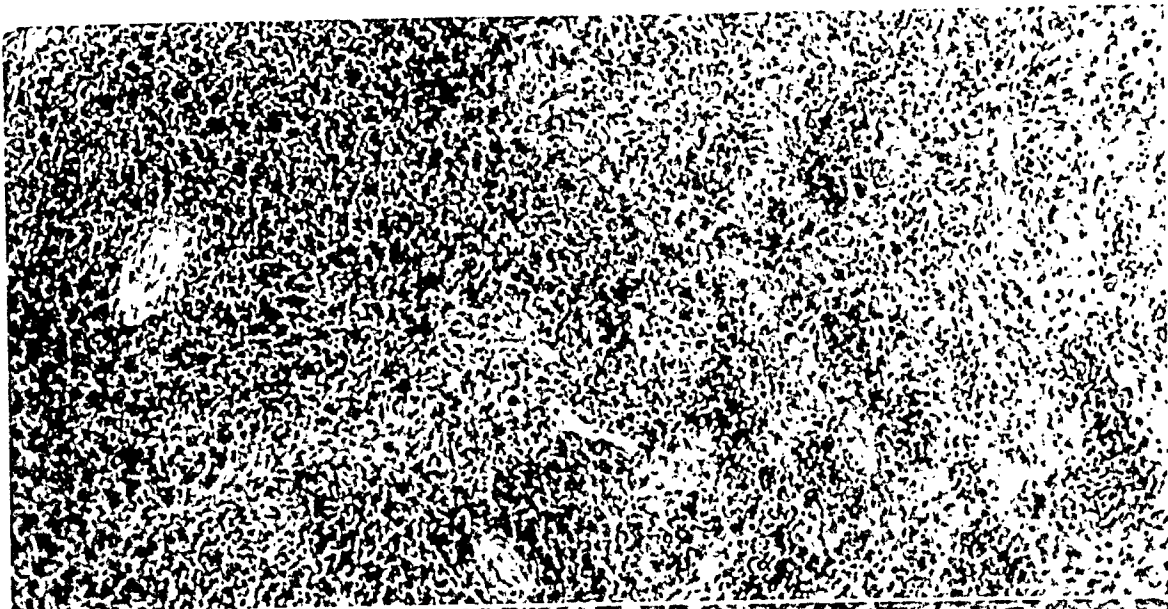
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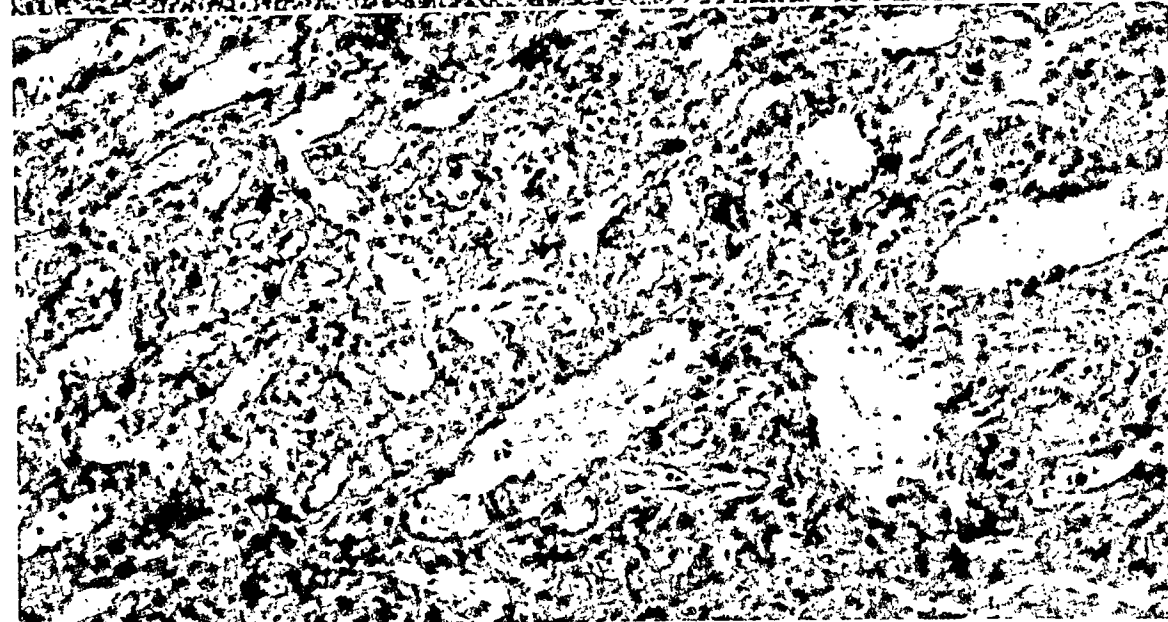
PLATE 113

- FIG. 56. Case 43. Duration of hepatitis, 20 days. Spleen. Hyperplasia of a follicle and of lymphoid tissue in pulp. $\times 50$.
- FIG. 57. Case 80. Duration of hepatitis, 30 days. Spleen. Marked engorgement of sinusoids, the walls of which have a rigid appearance. (See Figs. 19 and 41 for changes in the liver.) $\times 80$.
- FIG. 58. Case 108. Duration of hepatitis, 39 days. Spleen, showing depletion of lymphoid tissue; the follicle is atrophic. The sinusoids have rigid walls. $\times 50$.

6



7



58

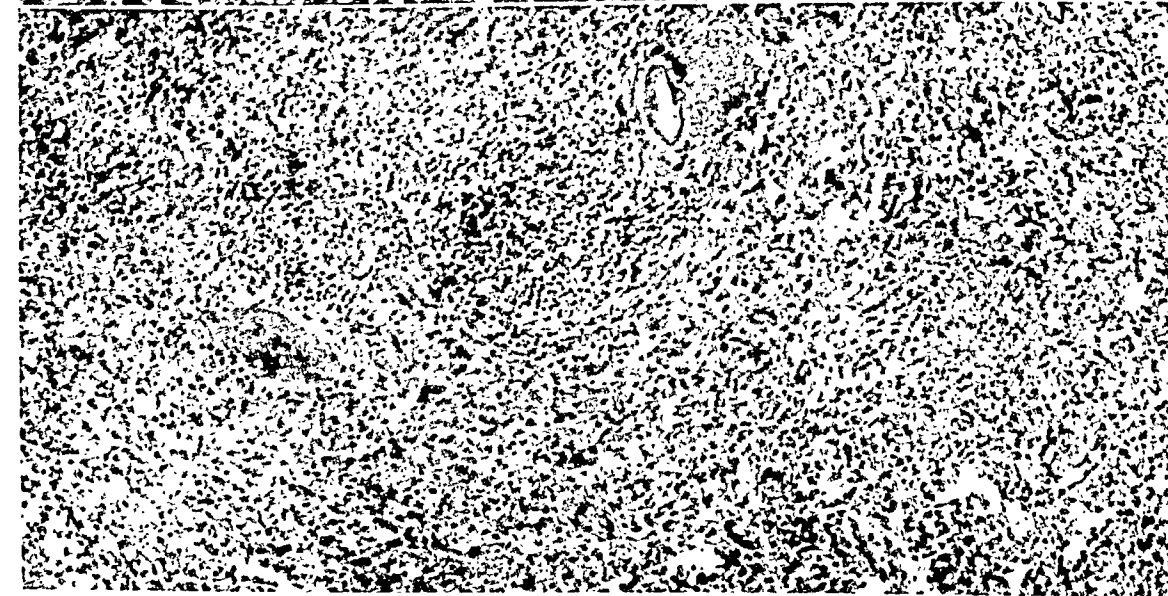


PLATE 114

- FIG. 59. Case 92. Duration of hepatitis, 67 days. Kidney, showing an intact glomerulus, and many tubules with bile casts. (A gross photograph of the liver of this case is shown in Fig. 9, and a photomicrograph in Fig. 44.) $\times 125$.
- FIG. 60. Case 84. Duration of hepatitis, 93 days. Several tubules are blocked with necrotic cells, beneath which is seen flat epithelium indicative of early regeneration. $\times 550$.
- FIG. 61. From the same case as Figure 60. In this tubule the necrotic cells have been removed. The lining epithelium is flat and has the appearance characteristic of early regeneration. $\times 375$.

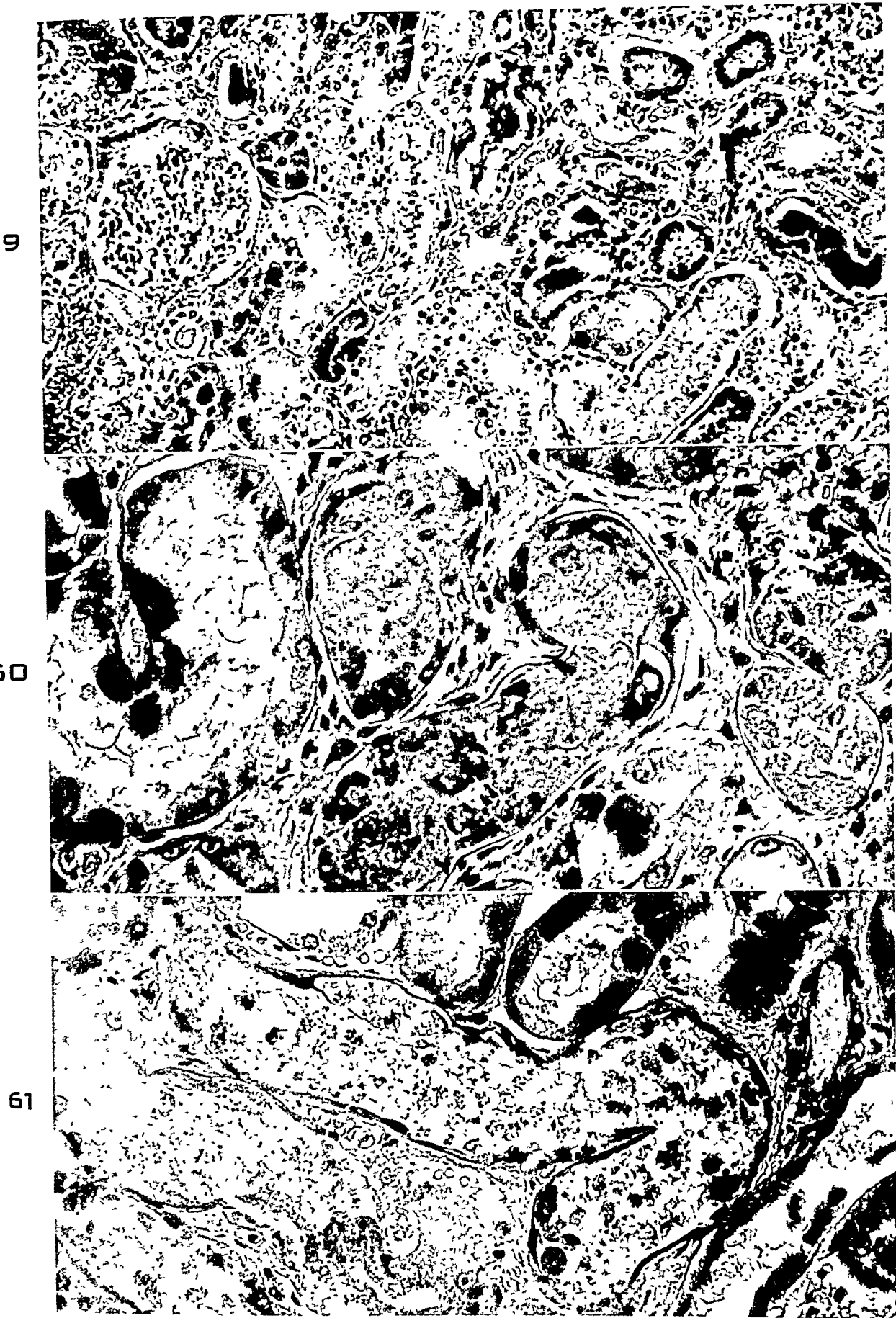


PLATE 115

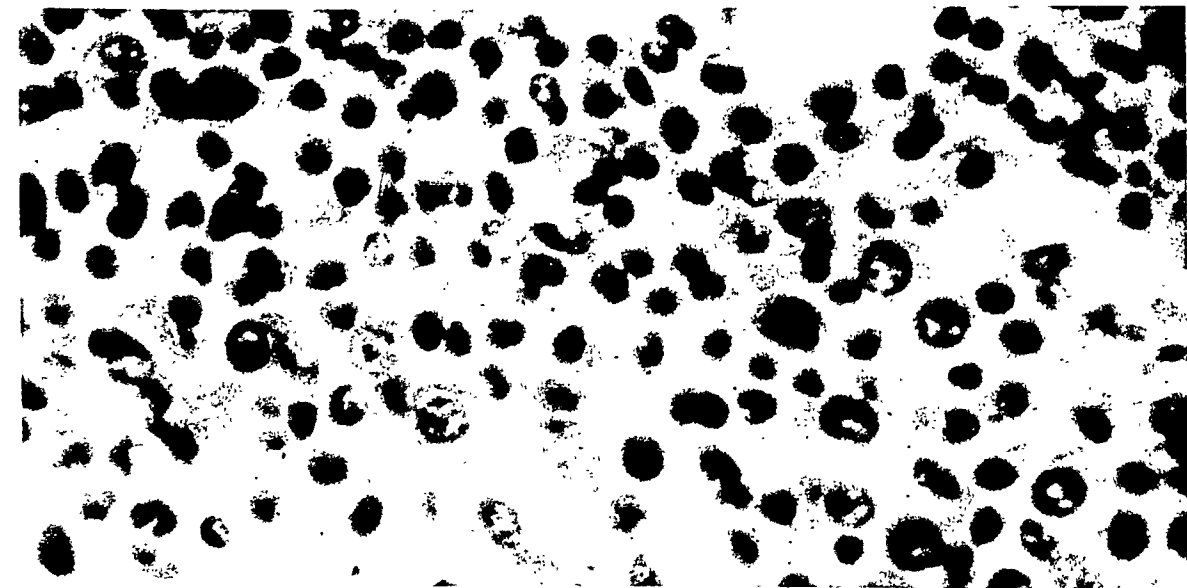
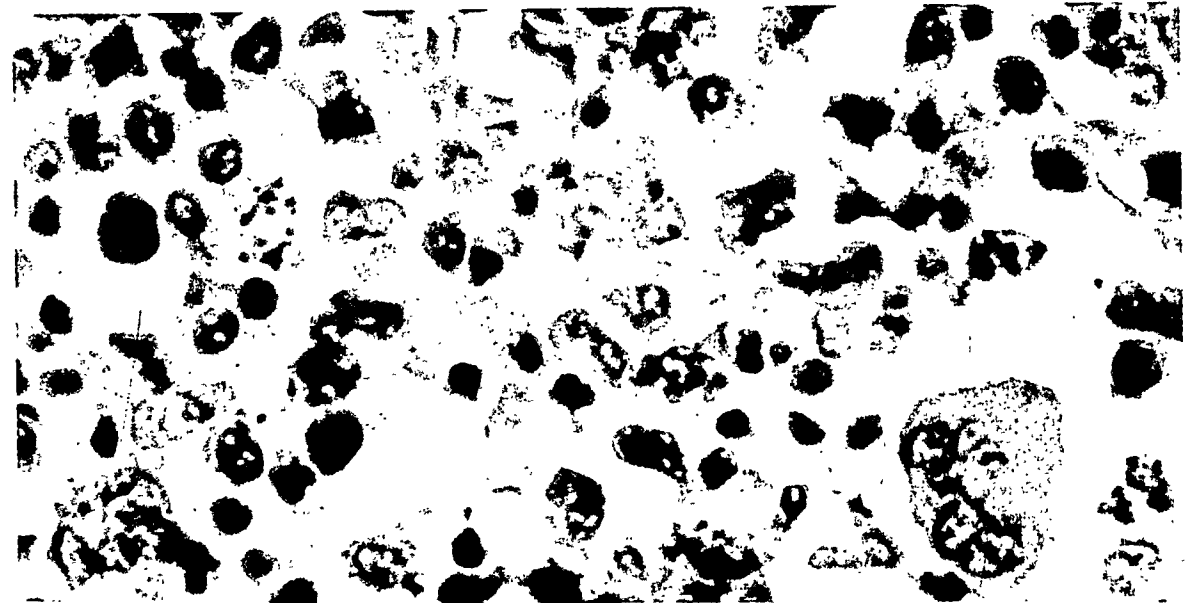
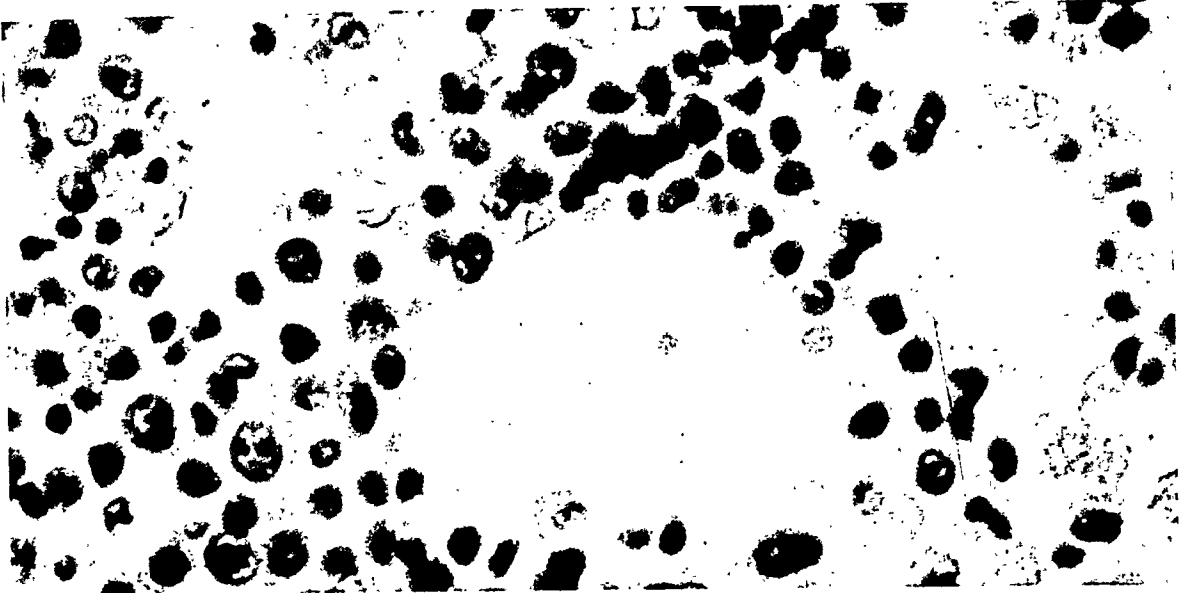
FIG. 62. Case 24. Duration of hepatitis, 36 days. Heart showing petechiae of epicardium and ecchymosis beneath the endocardium of the interventricular septum, near the bases of the aortic cusps.

FIG. 63. Colon with mesocolon and epiploic appendages, from case 24. An extensive hemorrhage is seen in the mesocolon.



PLATE 116

- FIG. 64. Case 94. Duration of hepatitis, 50 days. Bone marrow, showing a moderate degree of hyperplasia, particularly of the red cell series. $\times 450$.
- FIG. 65. Case 71. Duration of hepatitis, 49 days. Bone marrow, showing diffuse hyperplasia, particularly of the myeloid elements. $\times 450$.
- FIG. 66. Case 67. Duration of disease, 19 days. Bone marrow, showing marked hyperplasia, particularly of the red cell series. $\times 450$.



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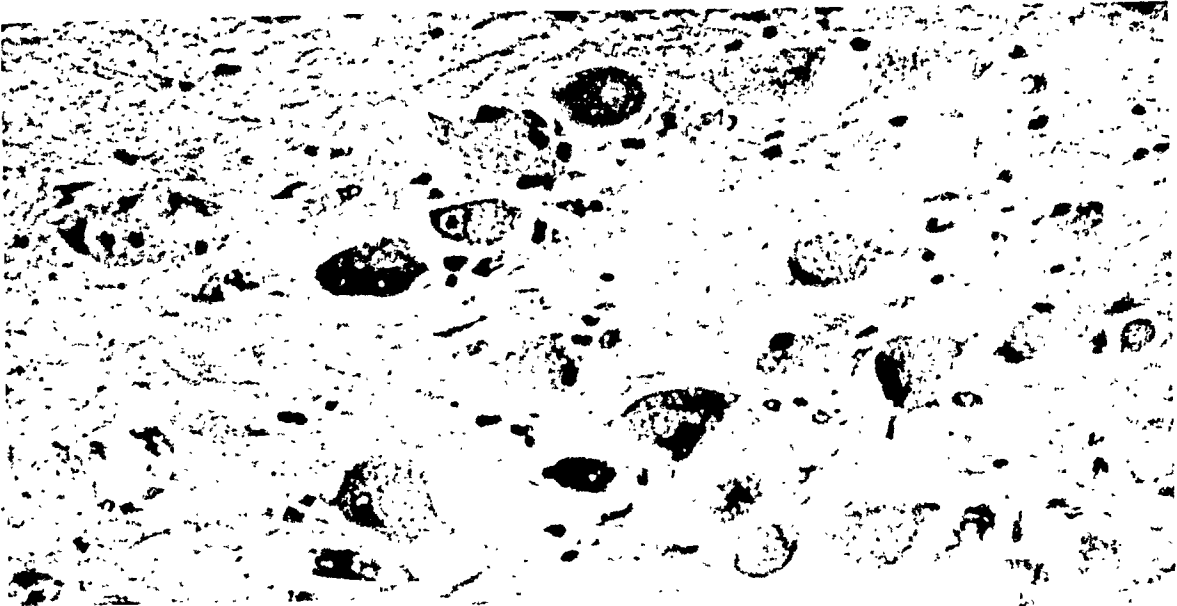
PLATE 117

FIG. 67. Case 76. Duration of hepatitis, 96 days. Base of brain; section through nucleus basalis. The ganglion cells show various stages of disintegration. There is no glial reaction. (For other changes in the brain of this case see Figs. 68, 69 and 76; the gross appearance of the liver is shown in Fig. 12, and a photomicrograph in Fig. 20.) $\times 200$.

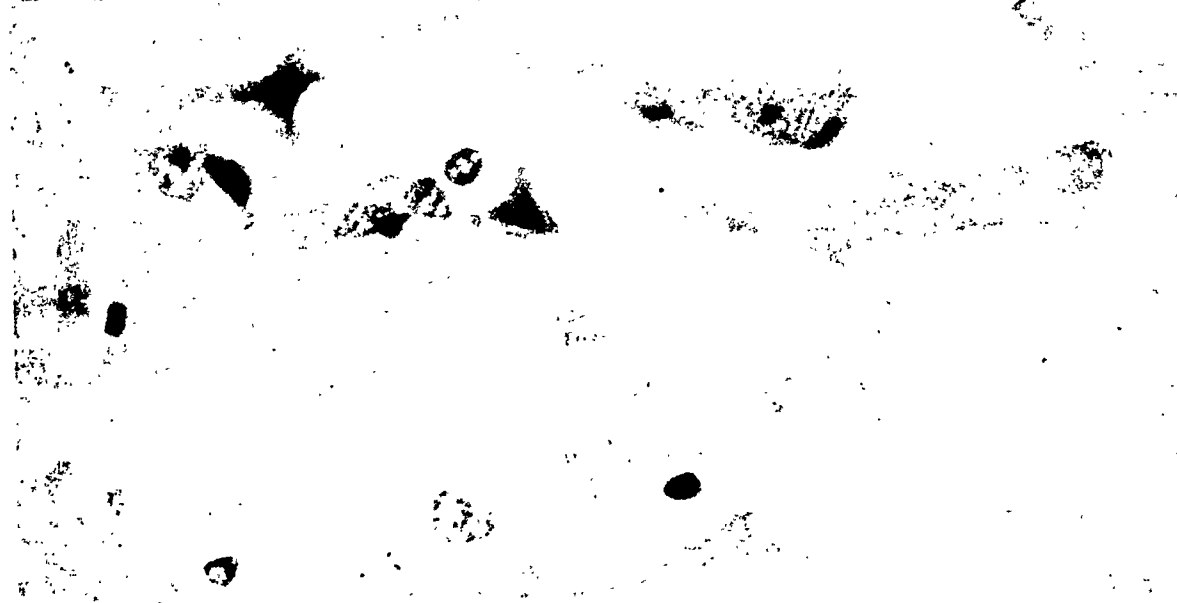
FIG. 68. Case 76. Brain; third layer of cortex. The photomicrograph shows three large ganglion cells. The upper cell has a broad apical dendrite and a well preserved nucleus and nucleolus. In the middle cell the apical dendrite is broadened; the nucleus has almost disappeared; the chromatin has been largely dissolved. The lower cell has been converted into a "ghost." (See Fig. 67.) $\times 800$.

FIG. 69. Case 76. Brain; section through midcortex. The ganglion cells have shrunken, densely staining bodies. The apical dendrites are prominent and tortuous. The change corresponds to "chronic" cell degeneration. (See Fig. 67.) $\times 680$.

57



58



69

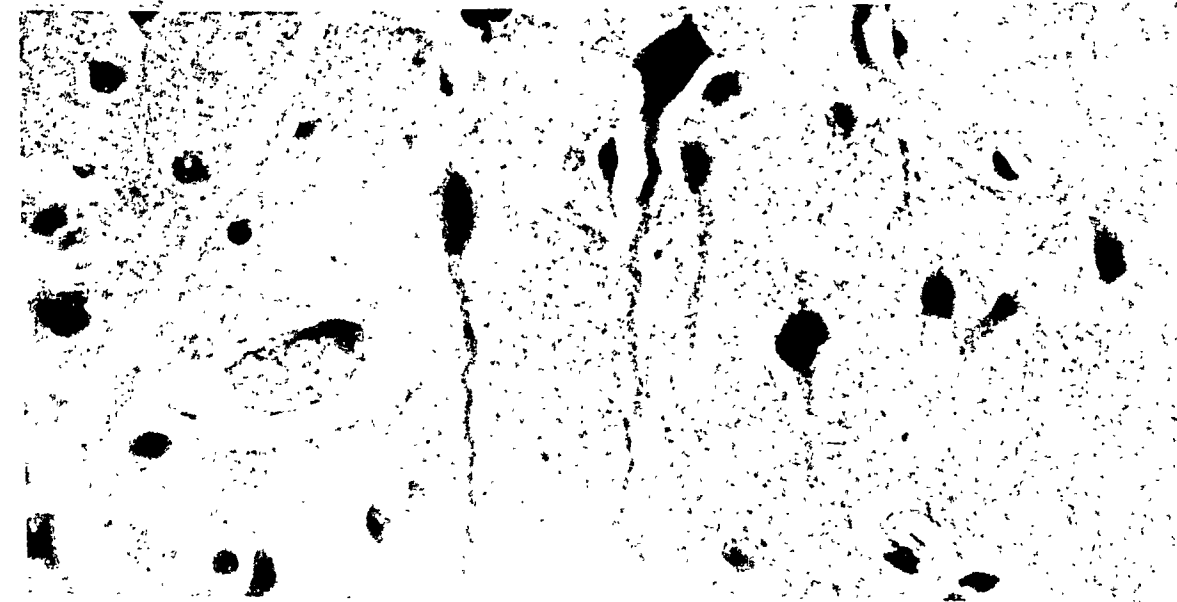
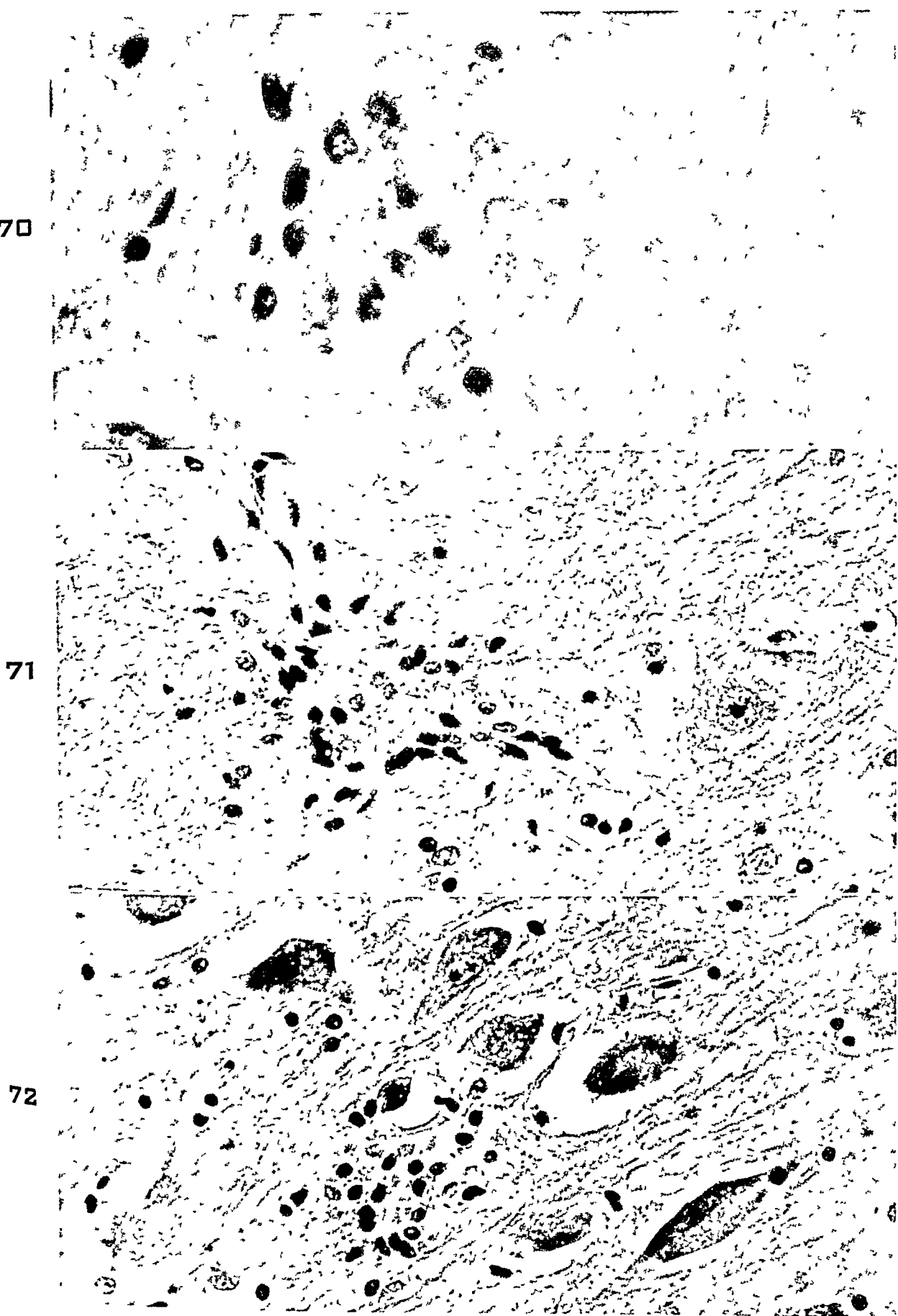


PLATE 118

FIG. 70. Case 86. Duration of hepatitis, 86 days. Brain; section through medulla oblongata. Invasion of a disintegrated ganglion cell by glial elements (neuronophagia). $\times 1000$.

FIG. 71. Case 84. Duration of hepatitis, 93 days. Brain; section through nucleus basalis. A disintegrated ganglion cell invaded by glial elements (neuronophagia). A nearby ganglion cell is intact. (Gross appearance of liver from this case is shown in Fig. 11, and photomicrographs in Figs. 5, 32, 37 and 46.) $\times 435$.

FIG. 72. Case 84. Brain; section through nucleus basalis. A small glial nodule has replaced a destroyed ganglion cell. The ganglion cells shown in the photomicrograph are in varying stages of degeneration. $\times 435$.

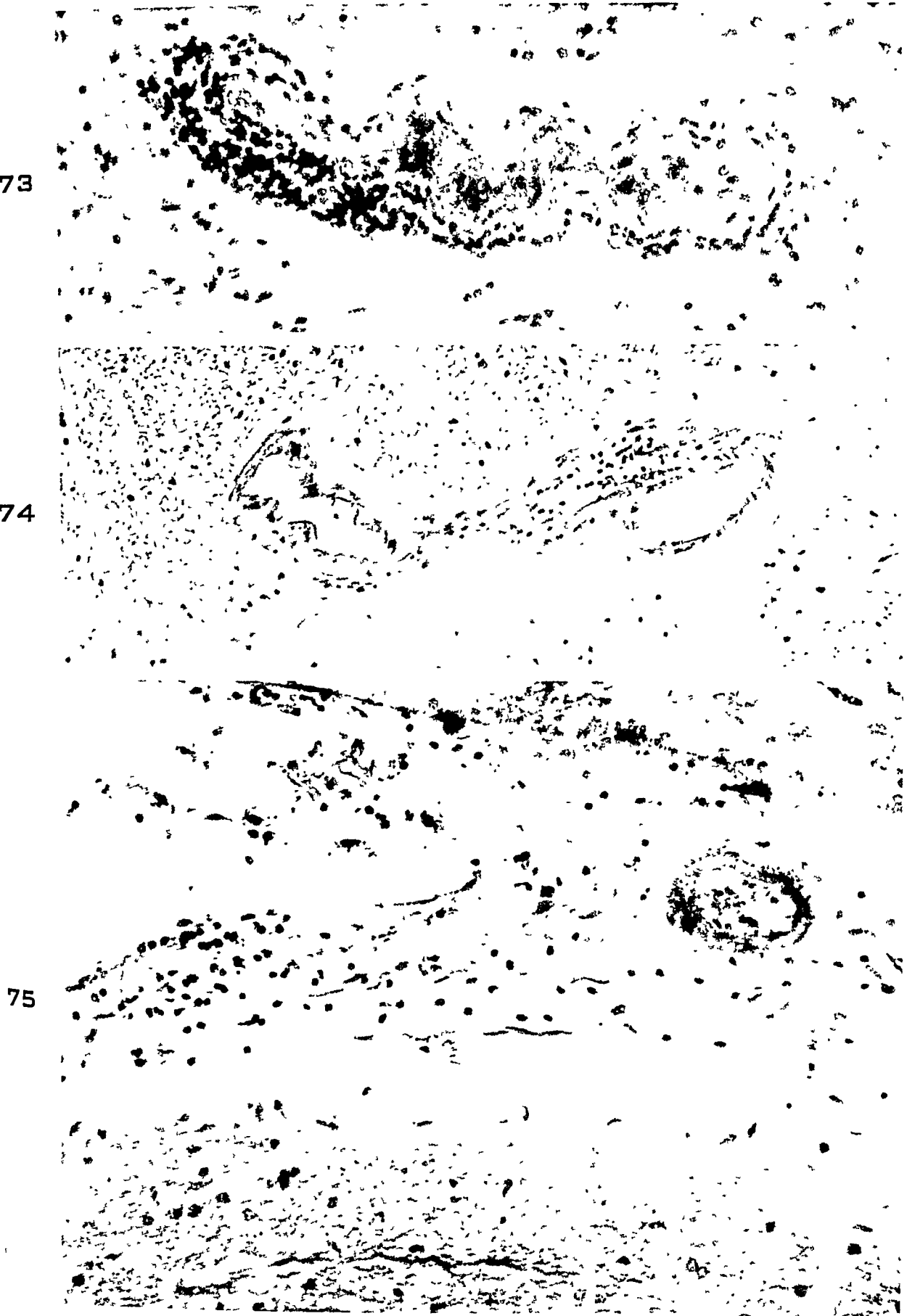


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Pathology of Fatal Epidemic Hepatitis

PLATE 119

- FIG. 73. Case 124. Duration of hepatitis, 37 days. Brain; periventricular system adjacent to thalamus with perivascular lymphocytic infiltration. The vessel involved is located beneath the ependyma of the third ventricle. (For reaction in meninges see Fig. 75; gross appearance of liver is shown in Fig. 10.) $\times 300$.
- FIG. 74. Case 78. Duration of hepatitis, 64 days. Tegmentum of pons. Slight perivascular lymphocytic infiltration. This represents the average degree of perivascular infiltration observed in the present series. $\times 175$.
- FIG. 75. Case 124. Brain. Mild degree of lymphocytic infiltration in leptomeninges; subpial edema. (See Fig. 73.) $\times 200$.

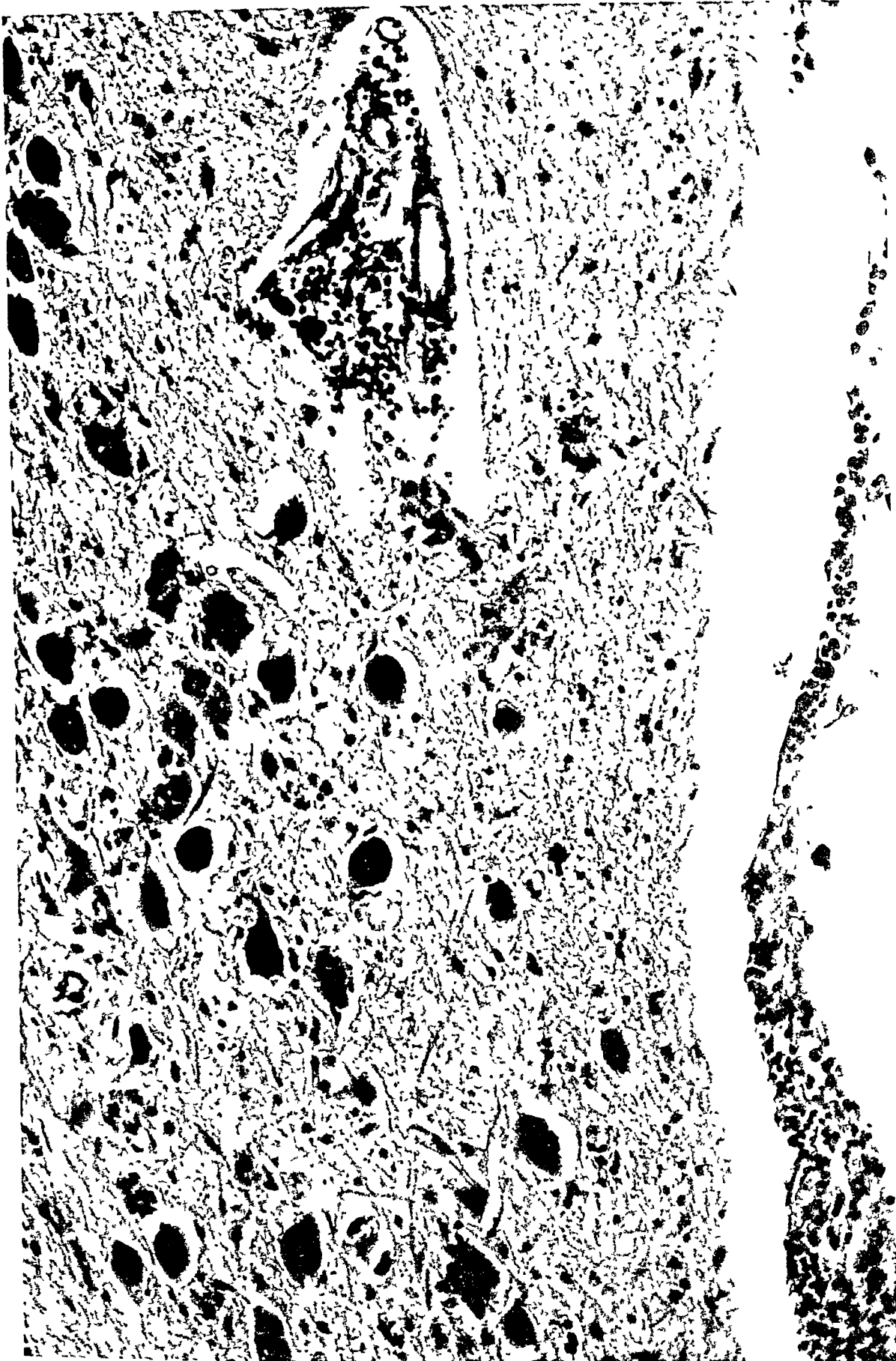


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Pathology of Fatal Epidemic Hepatitis

PLATE 120

FIG. 76. Case 76. Duration of hepatitis, 96 days. Brain; section through nucleus basalis lateral to anterior hypothalamic region. The meninges are infiltrated to a moderate degree with lymphocytes and histiocytes. In the subjacent cortex a similar infiltrate is noted around a small vessel. In nearly all ganglion cells the cytoplasm is swollen; in many the nucleus is shrunken and distorted. Around a few of the more disintegrated cells, satellitosis is evident. (See Figs. 67 to 69 for details of changes in ganglion cells.) $\times 240$.



76

THE STRUCTURE OF THE LIVER AFTER RECOVERY FROM EPIDEMIC HEPATITIS *

BALDUIN LUCKÉ, Lt. Col., M.C.

In the preceding paper,¹ the lesions produced by epidemic hepatitis were described as they occur in the liver and other organs in cases that terminated in death. The present paper is concerned with the far more numerous patients who recovered. What lesions, if any, remain in the liver, after the patient has been restored to health? Does the liver, when studied grossly and microscopically, show evidence of permanent damage, or, on the contrary, is repair complete, is lost tissue replaced, does healing occur without scarring? In a word, is clinical recovery accompanied by anatomic restitution so nearly complete as to justify the assertion that the liver has returned to its previous normal condition?

In order to answer these questions it was necessary to study patients who had recovered from a typical attack of epidemic hepatitis, and from whom later, as the result of accident or unrelated disease, the liver became available for examination. A series of such cases occurred during the outbreak of hepatitis in the Army in 1942. Of these, 14 cases have been studied. All these patients had typical hepatitis, the diagnosis being made by experienced clinicians during the course of an epidemic of the disease. Subsequent to the attack, 6 of the patients died from traumatic accident, and 6 from disease. In 2 other patients, a fragment of liver was removed during abdominal operations. These tissues were obtained from 1 to 14 months after clinical recovery from hepatitis.

To insure adequate sampling, blocks of liver were examined from a number of areas when possible. Sections from these were prepared by standard methods.¹ The pertinent clinical data and the results of the morphologic examination follow.

REPORTS OF CASES

Case 1

The patient was a white male, 27 years old.

Clinical Course. May 5, 1942: anorexia, weakness, constipation, headache, nausea, vomiting; later, jaundice. May 22: admitted; mildly jaundiced; liver not enlarged and not tender. May 24: appetite better; still complained of nausea; slight tender-

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ness over epigastrium. Improved steadily; by May 31 felt as well as before onset of illness, but trace of jaundice persisted; discharged from hospital. Temperature, pulse and respiration were normal throughout course.

Laboratory Findings. May 23: urine negative for albumin and sugar. Blood count: red blood cells, 5.0 million; white blood cells, 6,300; polymorphonuclear leukocytes, 41%; lymphocytes, 46%; monocytes, 9%; eosinophils, 1%; basophils, 1%. Icterus index, 75.

On June 15, 1942, this man was struck by an airplane and killed instantly. Duration of hepatitis, 26 days; interval between discharge and death, 16 days.

Post-Mortem Examination

Liver. Weight, 1810 gm. Surface was pale red and smooth; capsule, thin. Cut surfaces were homogeneous in appearance and showed no deviation from the normal.

Microscopically, the lobular pattern of the liver was accentuated because of infiltration of the periportal stroma with moderate numbers of polymorphonuclear leukocytes and lymphocytes. The reaction extended for some distance along the peripheries of some, but not of all, lobules. With connective tissue stains no increase in collagen formation could be demonstrated. The lobular architecture was everywhere normal. The hepatic columns were well oriented; the efferent veins occupied normal positions. Many efferent veins had somewhat swollen walls, but no increase in fibrous components was demonstrable. The bile canaliculi were inconspicuous. In the innermost region of some lobules a few liver cells were still lacking. The loss of parenchyma was minimal, probably much less than 1 per cent. Many cells, particularly in the central parts of the lobules, were binucleated, which indicates regenerative activity. The Kupffer cells in the central parts of many lobules contained yellowish pigment, probably lipofuscin.

This liver appears to be well on the way to complete restoration.

Case 2

This patient was a white male, 33 years old.

Clinical Course. About May 18, 1942: malaise, loss of appetite, nausea, vague abdominal pains, "dark" urine. May 16: admitted; skin and sclerae jaundiced; liver was 2 fingersbreadth below costal margin and slightly tender; icterus index, 75; white blood cells, 8,200. Progressed well during first 10 days in hospital. Hepatitis became quiescent, as was indicated by clearing of jaundice and return of index to within normal range. Course was afebrile throughout. On 10th day of hospital stay, temperature rose to 101° F. June 8: chill. June 11: a rough pre-systolic murmur; the condition was now regarded as subacute bacterial endocarditis, probably precipitated by the attack of catarrhal jaundice. June 27: died (50 days after onset of symptoms of hepatitis).

Post-Mortem Examination

Liver. Slightly smaller than usual. Cut surface showed no gross changes.

Microscopically, the lobular pattern was uniform throughout the organ. The periportal stroma, however, was infiltrated to a moderate degree with lymphocytes, polymorphonuclear leukocytes, and occasional pigmented histiocytes; no increase in collagen had taken place. The small biliary ducts were somewhat conspicuous. The hepatic cords converged in normal manner toward centrally placed, thin-walled veins. In general, the cells were well preserved and of uniform size. Around the central lobular vein the cellular arrangement was somewhat less uniform; and the size of the cells varied; here, large cells with prominent hyperchromatic nuclei, or with two nuclei, were common. An occasional bile "thrombus" was encountered in this region (Fig. 3).

Case 3

The patient was a white male, 30 years old.

Clinical Course. During April, 1942, had an attack of epidemic hepatitis. No clinical details are available. Presumably made a good recovery and returned to duty. On June 2, 1942, died from an unrelated disease: dementia praecox with marked cachexia and hypostasis of the lungs. Interval between discharge from hospital and death, approximately 3 months.

Post-Mortem Examination

Liver. Normal in size and shape; surface was smooth; cut surfaces were grossly normal.

Microscopically, organ was normal. There was no scarring. All traces of previous injury had disappeared. This liver may be considered as an example of the complete repair which in all probability occurs in the vast majority of cases of hepatitis.

Case 4

This patient was a white male, age unknown.

Clinical Course. June 23, 1942: anorexia. July 3: jaundice. July 7: admitted. Steadily improved under treatment and was discharged on July 10. August 12: died of gunshot wound. Duration of hepatitis, approximately 17 days; interval between discharge and death, 32 days.

Post-Mortem Examination

Liver. Weight, 1440 gm. Surface was smooth. Cut surfaces revealed no gross changes.

Microscopically, the organ showed evidence of extensive regeneration. The lobular architecture was preserved; most lobules had a normal structural pattern, *i.e.*, cords of hepatic cells converged toward a common efferent vein. The argentophilic reticulum was intact, and its fibrils were normally delicate. Here and there, however, considerable variation in the size and shape of the lobules was encountered; many were uniformly enlarged, while others showed an eccentric in-

crease in size, so that the shape was distorted. In all lobules the great majority of the cells had stored an abundance of glycogen, and their nuclei were normal in appearance. Proliferative changes were most evident in the neighborhood of the central veins and at the lobular peripheries, where many cells were large and had smooth cytoplasm without glycogen granules and with prominent hyperplastic nuclei; binucleated and multinucleated forms were commonly encountered.

Bile canaliculi were inconspicuous, and retention of bile within cells or within hepatic columns was not evident.

The periportal canals were normal. In most areas their stroma was normal in quantity and quality; here and there, however, it was somewhat more abundant, extended for a short distance along the lobular peripheries and was infiltrated with moderate numbers of histiocytes, lymphocytes and polymorphonuclear leukocytes. In such regions the small biliary ducts usually had undergone slight proliferative changes; that is to say, their number appeared to have doubled or tripled.

Occasionally, small clumps of histiocytes laden with lipofuscin were encountered within the periportal stroma or in the central zones of lobules. The pigment probably was derived from liver cells and served as an indicator of a disintegrative process long since passed.

In summary, the structural restitution of the liver was nearly complete. Traces of inflammatory reaction still lingered in the periportal stroma of some lobules. The hepatic cells were storing glycogen in a normal manner; there was no evidence of interference with the vascular supply or the biliary drainage.

Case 5

This patient was a white male, 23 years old.

Clinical Course. May 20, 1942: anorexia, headache, "dark" urine, constipation, later, jaundice. May 24: admitted; blood pressure, 124/80. Course in hospital was uneventful. July 3: discharged and returned to duty.

Laboratory Findings. May 24 and June 16: urine negative for albumin; positive for bile. July 3: urine negative for albumin and bile. May 24: red blood cells, 4.5 million; white blood cells, 7,700; polymorphonuclear leukocytes, 64%; lymphocytes, 36%. Icterus index: June 8, 30; June 16, 15.

July 20: Died as result of bullet wound. Duration of hepatitis, 43 days; interval between discharge and death, 17 days.

Post-Mortem Examination

Liver. Size and color were normal. Capsule was smooth. Cut surface showed normal architecture.

Microscopically, the liver showed well advanced repair. There was

complete preservation of the lobular pattern. The portal canals and their stroma were normal; no proliferation of smaller biliary ducts was evident. The hepatic columns radiated in normal manner toward the central efferent veins; the strands of supporting reticulum were unbroken. The appearance of the central parts of the lobules contrasted with that of the peripheral zones: many of the central cells were larger and had richly chromatic nuclei; binucleated cells were commonly encountered. These central cells obviously were newly formed by multiplication. In contrast, the peripheral cells were smaller, their nuclei less prominent, and their cytoplasm was laden with glycogen. In some lobules the central cells were still loosely arranged and the tissue contained a few scattered lymphocytes as indicators of past damage. Many of the efferent veins still had a swollen edematous wall, but endophlebitis, such as is commonly observed in cases terminating fatally, was not present.

The conspicuous feature in the central lobular regions was the number of large pigmented macrophages, probably mobilized Kupffer cells; they had ingested a dark brown granular pigment which gave no reaction with iron stains but did react with fat stains.

Repair of the liver may be considered practically complete (Fig. 4).

Case 6

The patient was a white male, age unknown.

Clinical Course. Early in July, 1942, complained of nausea and vomiting and later became jaundiced. July 12: admitted. Course uneventful. July 25: discharged and returned to duty.

September 9: killed in automobile accident. Course of hepatitis, approximately 25 days; interval between discharge and death, 45 days.

Post-Mortem Examination

Liver. Weight, 1795 gm. Surface was smooth. Cut surface showed no significant alteration.

Microscopically, the organ showed little evidence of previous damage aside from the large size and irregular shape of many lobules. The portal canals were normal and their supporting stroma was of average quantity and normally cellular except in a few areas where slight proliferation had led to the extension of thin stromal strands part way about adjacent lobules. Practically all lobules had a normal structural pattern. The cells everywhere were well preserved; in the central lobular zones there were occasional clumps of histiocytes containing lipofuscin; here, binucleated liver cells were common. Many efferent veins had slightly thickened walls. Restoration of this liver is practically complete (Fig. 7).

Case 7

This patient was a white male, 25 years old.

Clinical Course. During August, 1942, had an attack of acute catarrhal jaundice. No clinical details are available. October 18: was operated upon for acute appendicitis. October 22: suddenly went into shock and died as result of obstruction of right pulmonary artery by embolus, probably arising from thrombus in left hypogastric vein. Duration of hepatitis unknown; interval between discharge and death, approximately 2 months.

Post-Mortem Examination

Liver. Weight was approximately 1300 gm., and consistency was normal. Surface was smooth. Capsule was thin. Cut surfaces had normal color and showed normal architectural pattern. No evidence of pathologic change was found.

Microscopically, the architecture was normal. The portal canals and their stroma were completely normal. The hepatic lobules were of average size, and their cords converged in normal manner toward the centrally placed efferent veins. The individual liver cells were normal in size, shape and details of structure. The canaliculi were inconspicuous. No bile "thrombi" were evident. The efferent veins had normal walls. The sinusoids were well filled, and their lining was intact. Reticulum stains showed that the framework had a normal pattern. No traces of previous injury were observed in this liver; restoration following the attack of epidemic hepatitis was complete (Figs. 5 and 6).

Case 8

The patient was a white male, 31 years old.

Clinical Course. About June 13, 1942: loss of appetite, nausea, vomiting, headache, weakness, malaise, "dark" urine. June 19: admitted; sclerae and skin icteric; no tenderness over abdomen; liver and spleen not palpable. Stay in hospital uneventful. June 26: free of symptoms; felt well; jaundice disappearing. June 28: discharged in good condition though still slightly jaundiced.

Went on drinking bout and died on July 5 from acute alcoholism. The alcohol which was drunk was probably impure and unfit for consumption. Duration of hepatitis, approximately 15 days; interval between discharge and death, 7 days.

Post-Mortem Examination

Liver. Except for slight congestion, grossly normal.

Microscopically, the liver was involved in a uniform manner. The lobules presented a similar appearance; in each the columns of liver cells were normally arranged and converged toward a central vein. But the cells immediately surrounding the vein had been destroyed, so that the innermost part of each lobule appeared empty. At the central terminals of the columns the cells were large and had prominent hyperchromatic nuclei; many were binucleated; some had become detached. The cells here were obviously multiplying and restoring lost tissue.

Regenerative activity, however, was not confined to the lobular centers. At the periphery of each lobule many minute biliary ducts were seen at the terminals of the hepatic columns, and larger biliary ducts with numerous branches were present in the periportal stroma. The liver cells also were multiplying, as was indicated by the presence of many richly chromatic nuclei and binucleated cells. This liver exemplifies the fact that the peripheral zone next to the portal area usually takes an active part in the restoration of injured tissue.

Apart from the loss of cells and the multiplication of neighboring survivors, there were no noteworthy changes in the hepatic cords. The component cells had a somewhat lumpy cytoplasm, probably as a result of glycogen storage; no fat could be detected by appropriate stains. The nuclei were normal. The bile canaliculi were inconspicuous and contained no inspissated material.

The supporting reticulum was completely preserved, and where liver cells had been lost unbroken lines of reticulum swept toward the central vein. The latter, in most lobules, had a normal wall; occasional veins with somewhat thickened walls were encountered, but endophlebitis was nowhere seen. The sinusoids were patent and filled with blood.

An indicator of previous destruction of liver cells was furnished by the conspicuous number of swollen and pigmented Kupffer cells. Many had become detached and isolated or, in small clusters, lay in the stroma, particularly in the "empty" center of the lobules and in the periportal stroma. The pigment stained the cells diffusely; it occurred as small brown granules, gave no reaction for free iron, did not have the appearance of bile and stained deeply with Sudan and with silver. The latter, probably by encrustation, caused the granules to appear much coarser than they seemed unstained. This pigment was probably derived from the breakdown of liver cells; it belongs in the large and heterogeneous group of lipochromes.

The peripheries of the lobules were clearly marked, and here the portal stroma still contained a moderate excess of lymphocytes and plasma cells, occasional leukocytes and many pigmented histiocytes. The proliferative changes in the bile ducts, mentioned previously, helped in making the lobular peripheries prominent. The portal canals were normal. There was no evidence of connective tissue overgrowth. It is to be expected that the reactive changes will eventually subside.

Summarizing, this liver shows evidence of destruction of cells in the innermost portions of the lobules (Fig. 2). Through regenerative multiplication of the adjacent surviving cells all but approximately 5 per cent of the parenchyma has been restored. The small amount still lacking to complete restoration is negligible, in view of the enormous

reserve of hepatic tissue. What part alcohol and associated faulty diet played in the hepatic picture of this case is problematic. From the history it is evident that death was due directly or indirectly to excessive use of alcohol; moreover, the alcohol used was probably impure and unfit for consumption. There is a distinct possibility that because of excessive consumption of alcohol complete restoration of hepatic tissue has been delayed.

Case 9

The patient was a white male, 23 years old.

Clinical Course. May 22: anorexia, nausea, fatigue, constipation; later, "dark" urine. May 28: icteric sclerae. June 4: admitted; moderately jaundiced; slight tenderness in right upper quadrant; liver not palpable. The course was afebrile. Appetite remained poor for several days, then gradually returned to normal.

Laboratory Findings. Icterus index: June 8, 90; June 15, 50; June 17, 30. June 4: urine was positive for bile. June 5: red blood cells, 4.9 million; white blood cells, 4,700; polymorphonuclear leukocytes, 72%; lymphocytes, 28%.

October 29: killed in an automobile accident. Duration of hepatitis, 25 days; interval between discharge and death, 102 days.

Post-Mortem Examination

Liver. Grossly normal except for a traumatic tear through the capsule.

Microscopically, the architecture of the liver was preserved. The portal canals were normal. The cellular contents of the supporting stroma were within the normal range. The hepatic lobules had average size and shape; their cords converged toward centrally placed efferent veins. The latter usually had thin walls, though here and there a vein with a thick edematous wall was encountered. The individual liver cells were normal in staining qualities; occasional binucleated forms were present, particularly in the more central portions of the lobules. The reticulum framework was normal in arrangement and amount. This liver appeared to have been completely restored.

Case 10

This patient was a white male, 35 years old.

Clinical Course. About July 15 he was seen as an out-patient because of icteric sclerae, with the usual symptoms of catarrhal jaundice. Because of mild character of the attack, he was not placed in hospital. July 22: dyspnea and signs of bronchopneumonia developed. July 23: died.

This patient had an attack of mild epidemic hepatitis and a virulent form of hemorrhagic bronchopneumonia developed while he was recovering from the hepatitis. The total duration of the hepatitis is difficult to estimate from the history, but it was probably 2 weeks. No further information is available.

Post-Mortem Examination

Liver. Average size, had a smooth surface and thin capsule. Cut surface showed no significant deviation from the normal.

Microscopically, the architecture was preserved. The portal stroma was normally cellular; the bile ducts showed no proliferative changes. Small groups of liver cells had been lost in patches which were usually adjacent to the central lobular veins. In these regions the sinusoids were moderately engorged, and scattered histiocytes and lymphocytes were present. The efferent veins had somewhat swollen walls, some of which were sparsely invaded by lymphocytes. Active regeneration of liver cells in the destroyed areas was indicated by the presence of numerous binucleated and multinucleated cells. In many lobules the intracolumnar canaliculi were conspicuously dilated and contained clumps of inspissated bile.

This liver is an example of early restoration which is not as yet complete (Fig. 1).

Case 11

This patient was a white male, 35 years old.

Clinical Course. In June, 1942, became fatigued and was intermittently nauseated. During July, lost his appetite; tenderness developed in the upper abdomen; the urine became dark; and jaundice appeared, which gradually deepened. About August 1 the stools became clay-colored. Diagnosis of acute catarrhal jaundice was made on August 3. August 8: patient was transferred to a General Hospital; was nauseated and deeply jaundiced; complained of itching but had no other objective or subjective symptoms; blood pressure, 104/70. After 1 week in bed he improved considerably. September 2: felt much better; stools darker; liver slightly enlarged and tender. September 6: temperature, 100° F.; complained of discomfort in upper abdomen. September 14: no complaints; jaundice much improved; edge of liver no longer below costal margin. October 2: in good condition. From then on progress was uneventful. November 11: patient discharged and returned to duty.

On December 13, signs of perforated peptic ulcer developed. At operation the perforated area was found on the anterior wall. The liver had a normal appearance. The edge was slightly thickened. A specimen approximately 2 by 1.5 cm. was removed for examination. Duration of hepatitis, approximately 6 months; interval between discharge and taking of specimen for biopsy, 32 days.

Laboratory Findings.

Date	Icterus index	Date	Icterus index	Date	Icterus index
August 10	121	Sept. 6	43	Oct. 7	15
August 17	200	Sept. 12	31	Oct. 23	12
August 24	135	Sept. 21	26	Nov. 6	16
August 30	100	Sept. 30	23	Nov. 11	12

Blood Count. August 14: red blood cells, 4.2 million; white blood cells, 8,500; polymorphonuclear leukocytes, 59%; lymphocytes, 37%. October 30: red blood cells, 4.3 million; white blood cells, 8,800; polymorphonuclear leukocytes, 69%; lymphocytes, 31%.

Microscopic Examination of Specimen Removed from Liver

Microscopically, the specimen consisted of a triangular piece of tissue measuring 17 mm. at the base and 8 mm. in height. The capsule was of average thickness. Its vessels were engorged and a few capil-

laries had ruptured; the resulting small hemorrhages were probably due to the operative procedures. The architectural pattern of the liver was normal. The size and shape of the lobules were unaltered; the lobules were composed of normal hepatic cords which converged toward central efferent veins. The individual cells were of average size and their nuclei had a normal appearance; the cytoplasm was dotted with many small irregular vacuoles which indicated normal glycogen storage. Occasional cells contained a few sharply contoured droplets of fat. The reticular framework of the lobules was intact and was normally delicate. The efferent hepatic veins and the portal canals were likewise normal. The portal stroma was infiltrated by moderate numbers of lymphocytes and leukocytes. In some of the portal vessels, and here and there in the sinusoids, were small clusters of well preserved leukocytes which probably indicated a recent infection or destructive process in the abdomen. Hepatic damage had been successfully repaired, and restoration may be considered complete (Fig. 8).

Case 12

The patient was a white male, 25 years old.

Clinical Course. June 16, 1942: admitted to hospital with history of feeling tired and having poor appetite for past 2 weeks. Sclerae became jaundiced on June 15. On admission he was ambulatory and not acutely ill. Liver was not tender or palpable. Clinical course was uneventful and afebrile. Remained in hospital until December 15 and was then given sick leave. In January, 1943, upper abdominal pain developed which was not affected by food, activity, or pressure; he was not nauseated and did not vomit. February 13, 1943: x-ray examination revealed numerous stones in the gallbladder. Impression of the surgeons was that the stones originated during attack of acute hepatitis in summer of 1942. March 23: cholecystectomy showed the gallbladder had slightly thickened walls and contained seven dark brown stones. At this operation a small portion of the liver was removed for examination.

Duration of hepatitis, approximately 3 months; interval between discharge and taking of specimen for biopsy, approximately 4 months.

Laboratory Findings.

Date	Icterus index	Date	Icterus index	Date	Icterus index
July 7	230	August 1	32	Jan. 1	17
July 10	125	August 11	26	Jan. 8	18
July 19	41	Sept. 6	25	Jan. 11	18
July 24	49	Sept. 13	12		

Microscopic Examination of Specimen Removed from Liver

Two fragments of tissue, each measuring approximately .18 by 5 mm. were examined. Both were from the region of the gallbladder. The tissue changes in the two sections were somewhat dissimilar. In one, the architectural pattern was normal, although several lobules were exceptionally large. The portal canals and their supporting stroma

showed no alteration. The efferent veins had thin walls; occasional ones were eccentrically located. The liver cells generally were large and of uniform size; all were well preserved; their nuclei were intact and their cytoplasm contained a normal store of glycogen. In the other section thin strands of stroma partly encircled some of the lobules. Otherwise the appearances of the two sections were similar. The slight focal perilobular fibrosis was similar to that which commonly occurs in regions of the liver adjacent to a chronically inflamed gallbladder; it probably represented an extension of a local chronic inflammatory reaction. Restoration of the hepatic parenchyma was complete.

Case 13

The patient was a white male, 32 years old.

Clinical Course. About June 27, 1942, generalized aching, malaise, anorexia and nausea; later, jaundice and "dark" urine. July 3: admitted; temperature, pulse and respiration were normal; liver not definitely palpable and not tender. While in hospital jaundice deepened markedly. Patient remained afebrile except for occasional rises in temperature up to 99.2° F. September 1: discharged and given 30 days sick leave.

Laboratory Findings. On admission, icterus index was 25; it gradually increased during the next 3 weeks to a maximum of 230, after which it dropped; it was 10 at the time of discharge. During the early stages of jaundice, the urine contained bile. Blood chlorides on July 28 were 412 mg. %.

April 10, 1943: died from bullet wound. Duration of hepatitis, approximately 3 months; interval between discharge and death, 8 months.

Post-Mortem Examination

Liver. Weight, 1580 gm. External surface was smooth, capsule was thin, and cut surfaces were grossly normal.

Microscopically, the lobular pattern was completely normal. The size of the lobules in general varied but little from the average; in occasional areas a few lobules appeared enlarged, and a few others were reduced in size. The portal triads also were normal; most of them lay in a scanty stroma which here and there contained a slightly increased number of lymphocytes. The hepatic cords converged in regular manner toward thin-walled, centrally placed veins. The liver cells were fairly uniform in size; their nuclei were well preserved; their cytoplasm had an abundant store of glycogen. Only one indicator of previous damage remained: in some lobules the cells immediately adjacent to the central veins were large and had prominent, deeply chromatic nuclei; binucleated cells were commonly encountered.

Case 14

This patient was a white male, 22 years old.

Clinical Course. July 7, 1942: loss of appetite, general malaise, nausea, vomiting, "dark" urine; later, jaundice. Uneventful course in hospital. July 24: discharged.

Patient was readmitted about 1 year later with evidence of chronic glomerulonephritis and died on September 24, 1943. Diagnosis was confirmed by post-mortem examination. Duration of hepatitis, approximately 17 days; interval between discharge and death, 14 months.

Post-Mortem Examination

Liver. Grossly normal.

Microscopically, the lobules were normal in size, shape and arrangement. The periportal stroma was scanty and contained no excessive number of cells. The bile ducts and vessels were normal. The hepatic cords had the usual radiating pattern, and their component cells were normal. The efferent veins had thin walls. Repair of this liver was complete.

COMMENTS ON THE GROSS AND MICROSCOPIC APPEARANCE OF THE LIVER

Without exception, the liver in each of the 14 cases studied had macroscopically a normal appearance. The size and shape were within normal limits, the surface was smooth, the capsule thin, the consistency unaltered. The structural pattern of the cut surface was uniform.

Microscopically, the appearance varied somewhat, depending on the length of time between the attack of hepatitis and death or biopsy. In all cases, however, the lobular architecture was preserved, and the reticulum frame was intact.

In summarizing the microscopic appearances it is convenient to describe first the hepatic parenchyma, and afterwards the periportal stroma, ducts, and vessels.

The Hepatic Parenchyma

In 2 cases, restitution of lost parenchyma was not yet complete. One of these patients (case 10) had died of intercurrent infection during convalescence from hepatitis, the other (case 8) from acute alcoholism only 1 week after leaving the hospital. In these livers the process of repair could still be observed.

Thus in case 10, in the central portions of most lobules, the columns of liver cells appeared broken, and small patches of parenchyma were lacking (Fig. 1). Many bile canaliculi were dilated with clumps of bile. Numerous binucleated or multinucleated liver cells indicated active regeneration.

With the exception of these two examples of incompleated repair, restitution of hepatic parenchyma was very nearly complete in 3 cases, and entirely complete in the other 9. The patients (cases 1, 2 and 5) of the first group died within approximately 3 weeks after clinical re-

covery from jaundice. The lobular structure in all had been restored completely, and only an occasional liver cell was still lacking. Some traces of previous damage, however, were discernible. Thus, in case 2 numerous large cells with one or two hyperchromatic nuclei were clustered in the immediate neighborhood of the central lobular vein, and a few canaliculi in this region still contained bile "thrombi" (Fig. 3). The appearance of the reticulum in the central zone of a lobule, *i.e.*, in the previously damaged region, is shown in another, similar case (Fig. 4). The arrangement, delicacy and complexity of the reticulum network are entirely normal.

We now come to the group of 9 cases in which the lost tissue was entirely restored. In these cases a longer time, from 1 to 14 months, had elapsed since discharge from the hospital. In most of them the structure of the lobules was normal, while in 2 cases slight variations in size and shape of some of the restored lobules suggested previous injury and subsequent repair. The hepatic cells had a healthy appearance. Fat and glycogen storage appeared to be within the usual limits, and the cytoplasm contained no abnormal constituent. In summary, restitution of lobular parenchyma was very nearly complete 3 weeks after recovery from hepatitis, and entirely complete 1 month after clinical recovery.

The Periportal Stroma

A slight to moderate increase in cellularity was observed in nearly one-half the cases. The cells were mainly lymphocytes and larger mononuclear cells, but polymorphonuclear leukocytes were also present, although in relatively small numbers. This increase in cellularity was generally confined to the livers of those patients who had recovered less than a month previously.

In 3 cases of the series (1, 6, and 12) thin strands of cellular connective tissue were found to extend for some distance along the periphery of the lobules. Encircling of lobules or significant scarring was observed in none. Moreover, the slight fibrosis was focal and never diffuse.

Biliary Ducts

In 3 cases the small bile ducts showed a slight to moderate degree of proliferation. Conspicuous branching, such as is a prominent feature in fatal cases, occurred in none.

Vasculature

The branches of the portal vein and of the hepatic artery were normal. The sinusoids had an average blood content. The central lobular vein in 4 cases had somewhat swollen walls; in one instance

(case 10) the subendothelial intima was sparsely infiltrated with lymphocytes (this patient died during early convalescence). Definite endophlebitis, a notable feature in fatal cases, was not observed. None of the cases showed perivenous condensation of reticulum or of collagenous connective tissue.

Histiocytes with Lipofuscin Granules

In 5 cases pigmented histiocytes, isolated or in small clusters, were found, particularly in the central zones. These cells may be regarded as indicators of past destruction of liver cells.¹

SUMMARY OF MICROSCOPIC FINDINGS

The results of microscopic examinations may now be summarized as follows. In all 14 cases of the series, the lobular architecture was preserved, and the reticular framework was intact. Two patients who had died during, rather than after, convalescence showed incompleting repair, in the sense that small patches of hepatic parenchyma were still lacking in the central zone of the lobules.

In the remaining 12, restitution of the parenchyma was very nearly complete in 3, and entirely so in 9 cases. In the periportal stroma traces of inflammatory reaction lingered in 6 cases; in 3 of them slight focal increase of the stroma had taken place. Scarring was present in none. Slight proliferation of the small bile ducts was observed in 3 cases. Phagocytic cells containing lipofuscin were found in 5 cases. In 4 cases the walls of the central lobular veins were somewhat thickened. Briefly, the changes observed represent slight traces of preceding hepatic injury; they do not indicate persistent or progressive damage. The hepatic parenchyma has been restored in normal manner.

DISCUSSION

The liver is known to have great powers of regeneration.²⁻⁴ Whether after destruction of liver substance regeneration is complete, with restoration to the previous normal condition, or whether extensive scarring and permanent damage occurs, depends on two circumstances.⁵⁻⁸ The first is whether the damage is confined to the cells of the hepatic parenchyma. If so, regeneration may be complete, as these cells have great ability to multiply and restore themselves. If, however, damage involves the reticulum of the lobule or if the hepatic veins or the portal vessels and their stroma are destroyed, then restoration of the hepatic lobule occurs in an abnormal fashion, with more or less extensive fibrosis, and permanent damage.

The second factor is whether damage to the liver occurs only once

or whether insults are repeated. Recovery from a single injury affecting only the parenchymal cells may be complete whereas repeated destruction of cells, especially at short intervals, may result in fibrosis and permanent damage.

Such is the pattern of reaction of the liver to injury, as ascertained both through experimental work and from study of human material.

Thus Whipple and Sperry⁹ found that after chloroform had been administered to dogs in amounts sufficient to cause necrosis of two-fifths or three-fifths of every hepatic lobule, the livers of surviving animals regenerated perfectly in 3 weeks. Similar complete recovery of the liver occurred after single doses of carbon tetrachloride (Cameron and Karunaratne⁸), though not after repeated doses unless time for regeneration was allowed between doses.

In monkeys infected with yellow fever (Klotz and Belt⁶), two-thirds died and showed extensive liver necrosis, but of those that recovered all showed complete and scarless hepatic regeneration.

That the liver of epidemic hepatitis conforms to this reaction pattern has been shown by the present study. In hepatitis the destruction of liver cells occurs acutely, not as a continued process with progressive damage and fibrosis. Further, destruction is confined to the hepatic cells; reticulum, intralobular vasculature, portal canals and stroma are left intact. Therefore, complete regeneration is possible. The results of this investigation show that complete regeneration is in fact the rule; that in nonfatal cases of hepatitis there is no progressive or residual damage to the liver; that just as clinical recovery is complete, so the liver parenchyma is restored to its previous anatomic condition.

There have recently appeared two important papers^{7,10} on the pathology of the liver in epidemic hepatitis. In a number of patients, specimens for biopsy were taken both during the acute attack and after recovery. At the first biopsy there were many necrotic liver cells in the center of the lobules, but at the second biopsy the liver was found restored to normal, as is shown by photographs. The authors concluded that most cases of hepatitis end in complete recovery of the liver. In a few other cases, scars were found. The histories of these patients suggest that the scarring antedated hepatitis or else that the patients suffered from liver diseases other than hepatitis. Furthermore, a sharp distinction must be made between harmless focal scars and cirrhosis, a progressive disease affecting the liver diffusely. This distinction has lately been re-emphasized in an excellent paper by Karsner.¹¹

Lastly, there is a wealth of clinical evidence which favors the view that acute hepatitis, either in its epidemic or its sporadic form, tends to heal without leaving a permanently damaged liver such as is found

in cirrhosis. There has been no increase in cirrhosis following the numerous outbreaks of hepatitis. In fact, Rössle¹² stated that during the first World War and in the years immediately following, 1914 to 1922, the incidence of cirrhosis noticeably decreased, whereas during the same period occurred a rise in the incidence of so-called catarrhal jaundice.

It must not be forgotten that both epidemic hepatitis and cirrhosis of the liver are common diseases; hence patients suffering from cirrhosis may sometimes give a history of a previous attack of "catarrhal jaundice." Such a history does not, however, prove a causal relationship.

SUMMARY

Only a small fraction of the cases of epidemic hepatitis terminate in death. The great majority of patients make a clinical recovery that is complete and apparently permanent. Whether in these recovered cases the liver is fully restored to a normal condition, or whether, on the contrary, there is residual damage or even progressive pathologic changes is the subject of this investigation.

The structure of the liver was studied in 14 cases after recovery from epidemic hepatitis. From 1 week to 14 months after the attack, these livers became available for examination as the result of fatal accident or unrelated disease.

Grossly all livers appeared entirely normal. Microscopically the appearance varied somewhat with the elapsed time since recovery, but in every instance the integrity of all liver lobules was preserved. In 2 patients who died of intercurrent disease during convalescence, repair of the liver lobules was still under way, and cells lost from the central part of the lobules had not been entirely replaced. In 3 cases examined within a month after clinical recovery, the liver lobules were entirely reconstituted, but slight evidence of previous damage still remained. In 9 other cases examined from 1 to 14 months after recovery, the liver parenchyma was restored completely. In less than half of the cases, traces of previous damage were found in the portal triads, but in none was found significant scarring.

It is concluded that complete restoration of hepatic parenchyma occurs in nonfatal cases of hepatitis. This conclusion is in agreement with what is known about the ability of the liver to regenerate. Regeneration is usually complete providing that destruction is acute and injury not continued, and providing that destructive changes involve only the hepatic cells, not the framework or vessels. This is the case in epidemic hepatitis. In the present investigation there was found no evidence of permanent damage to hepatic parenchyma, and restoration of the liver was practically complete.

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[Illustrations follow]

DESCRIPTION OF PLATES

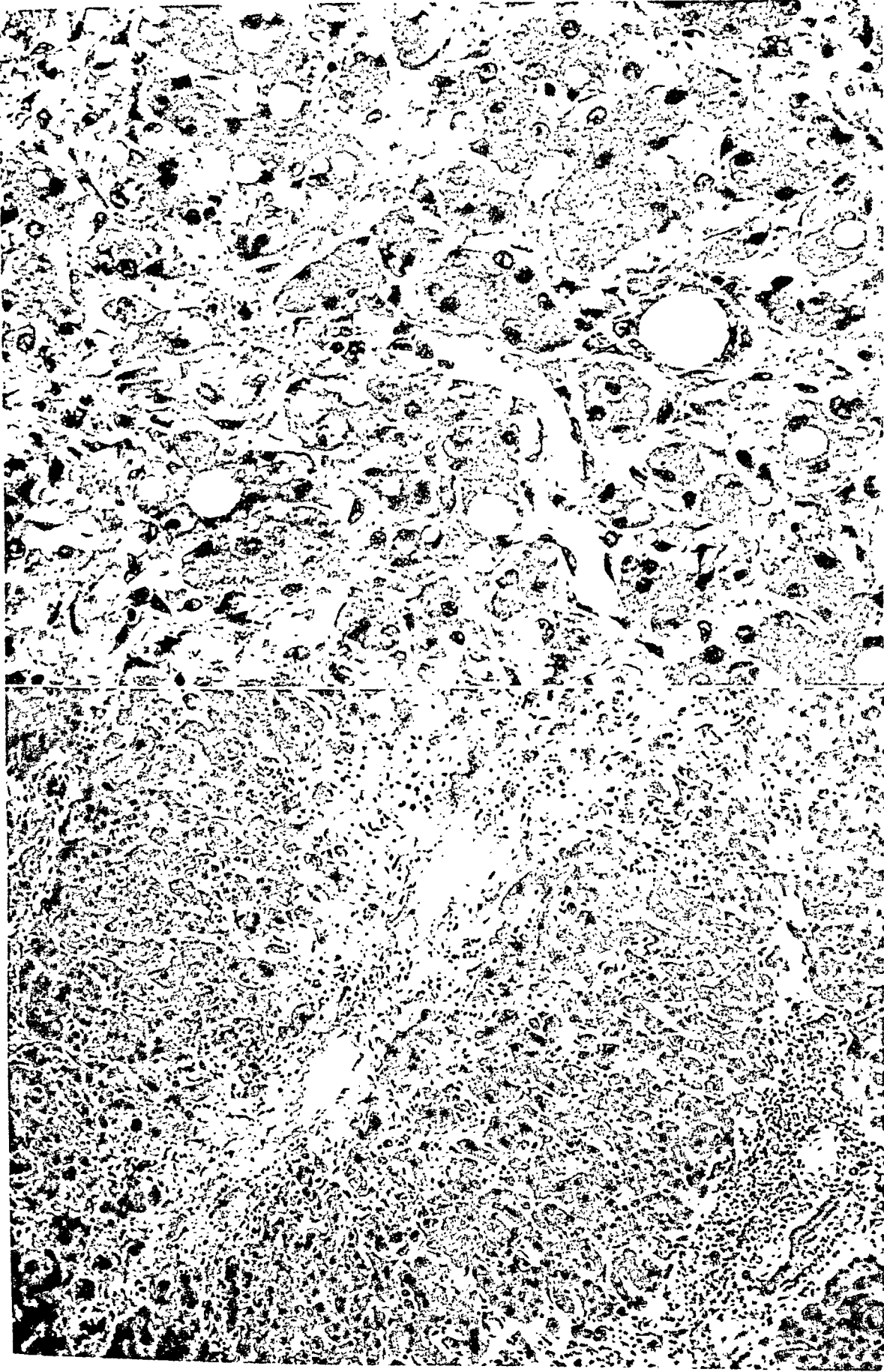
PLATE 121

FIG. 1. Case 10. Area from central part of a lobule in which restoration of parenchyma is incomplete; small groups of liver cells are lacking. The sinusoids are distended. The stroma is edematous, and through it are sparsely scattered lymphocytes and histiocytes. In two hepatic columns, shown in cross section, the canaliculi are dilated with bile. $\times 500$.

FIG. 2. Case 8. In the central part of this lobule the destroyed parenchyma has not as yet been completely restored. The hepatic cords converge in normal manner toward the lobular center. At the terminals of the cords the cells are large, and have prominent hyperchromatic nuclei; these regenerating cells are invading the empty stroma. The latter contains a moderate number of lymphocytes and histiocytes. The periportal stroma shows similar cells, and a few small proliferating bile ducts. There is no evidence of new formation of collagenous connective tissue. $\times 100$.

1

2



Lucké

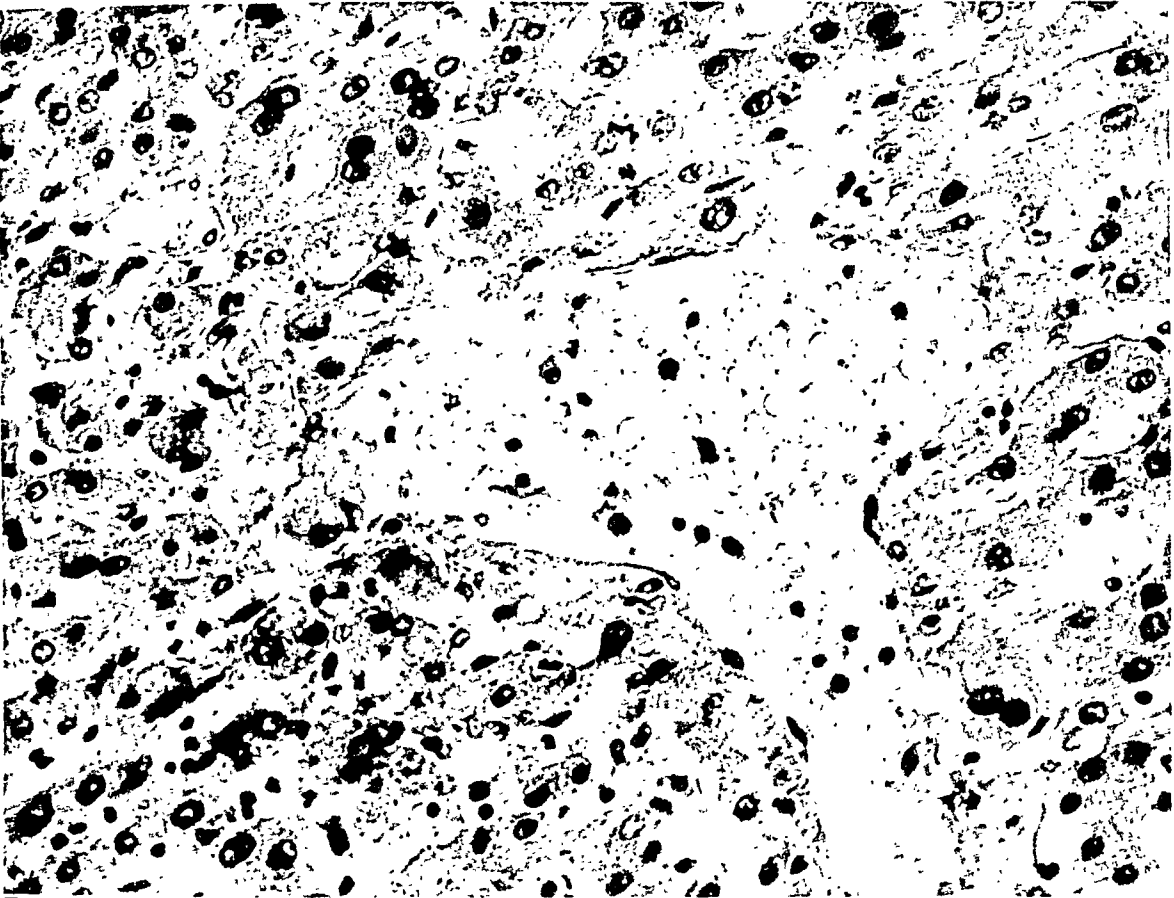
Recovery from Epidemic Hepatitis

PLATE 122

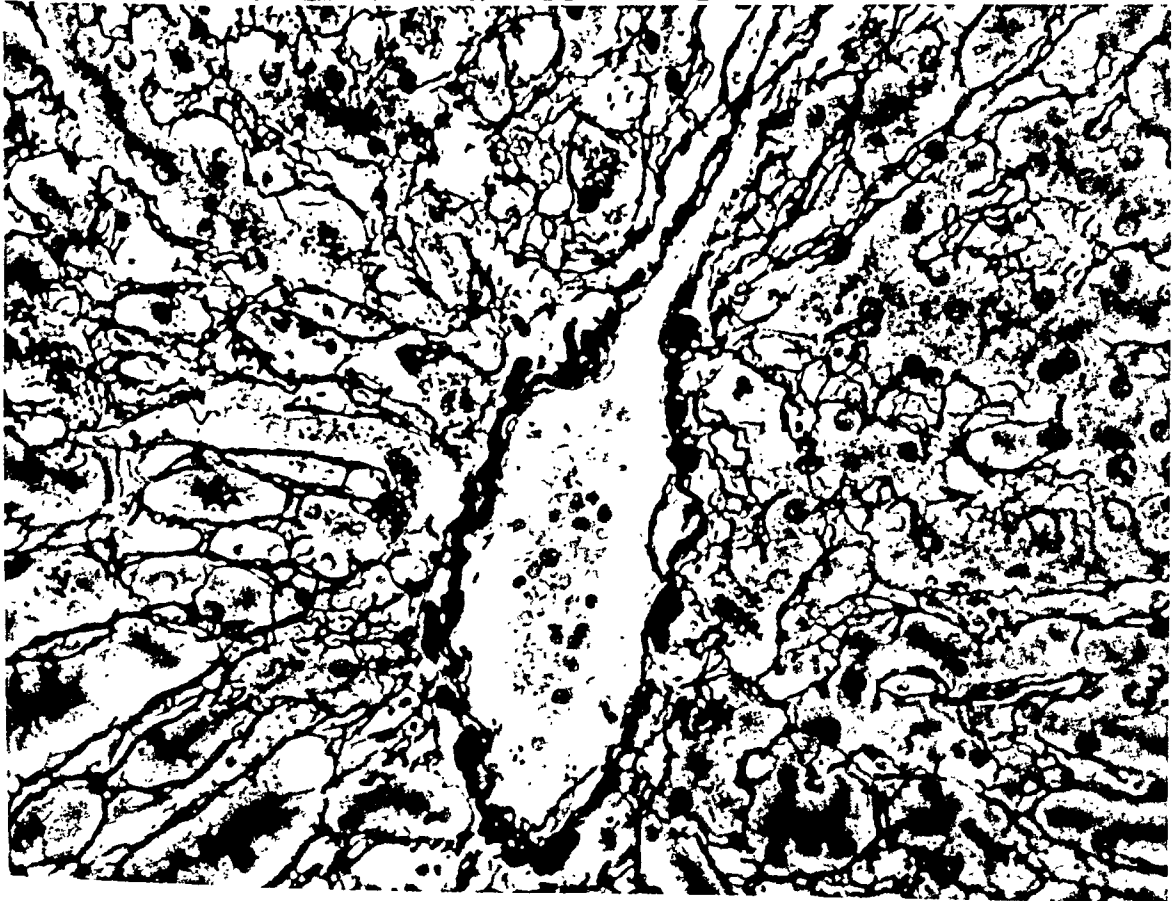
FIG. 3. Case 2. Central part of a lobule showing an efferent vein and the adjacent hepatic parenchyma. The wall of the vein is normal. The parenchyma has been restored; a number of liver cells are conspicuously large and have one or two prominent hyperchromatic nuclei. In one of the hepatic cords a bile "thrombus" may be seen above and to the left of a large vein. $\times 500$.

FIG. 4. Case 5. Central part of a lobule. The reticulum has a normal pattern. Here and there, a few liver cells are still lacking. The stroma contains numerous macrophages with ingested lipofuscin, the granules of which are blackened by the silver stain. Elsewhere, the reticular meshes enfold normal regenerated liver cells. Wilder's reticulum stain. $\times 500$.

3



4



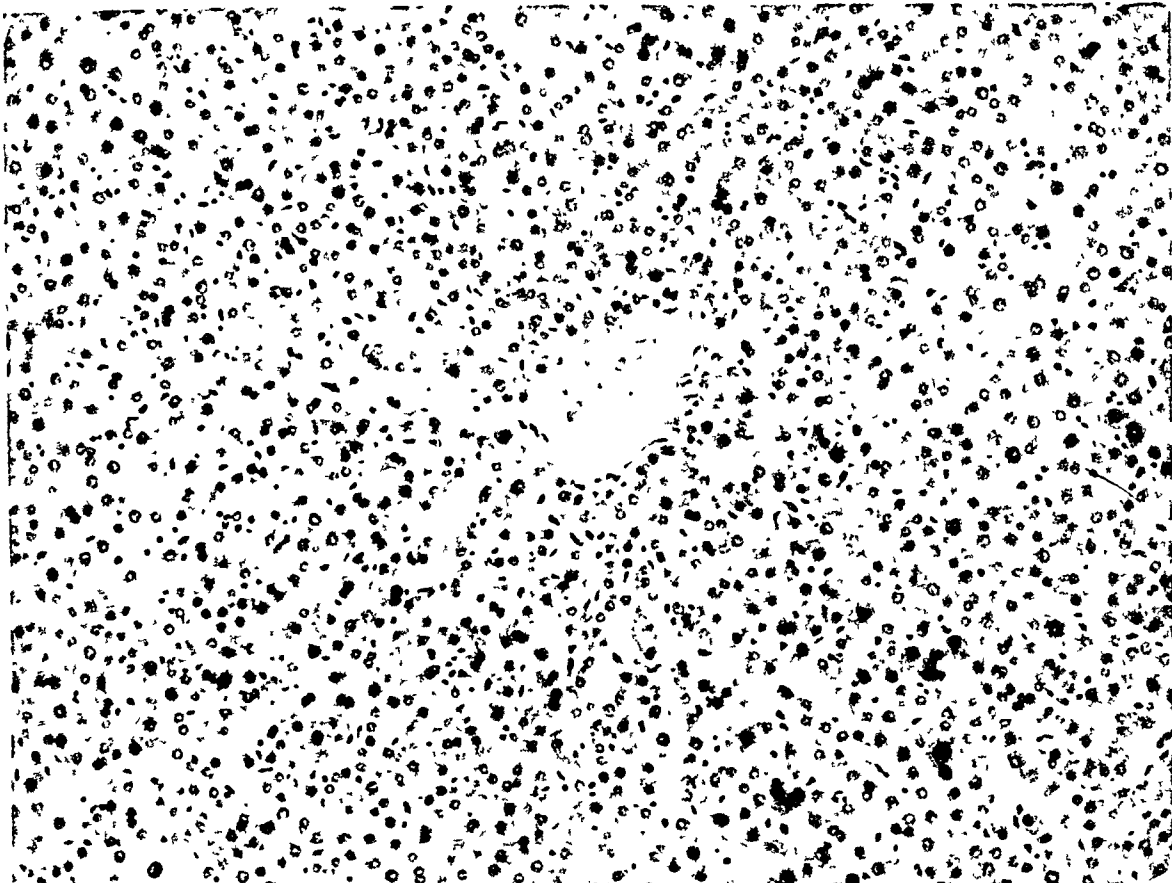
Lucké

Recovery from Epidemic Hepatitis

PLATE 123

- FIG. 5. Case 7. A hepatic lobule with columns of normal appearing hepatic cells converging toward a thin-walled central vein. No traces of previous injury can be observed. Restoration following the attack of epidemic hepatitis is complete. $\times 150$.
- FIG. 6. Case 7. Another lobule from the liver shown in preceding figure. The section has been stained by Wilder's method. The reticulum framework has a normal pattern of arrangement; its meshes enfold normal liver cells. $\times 150$.

5



6



Lucké

Recovery from Epidemic Hepatitis

PLATE 124

FIG. 7. Case 6. Central part of a lobule showing efferent vein, converging columns of liver cells and reticulum frame. The pattern of arrangement is normal. Restoration of this liver is practically complete. Wilder's reticulum stain. $\times 275$.

FIG. 8. Case 11. Hepatic lobule, showing normal pattern of arrangement of cell cords and reticulum. Restoration of structure is complete. Wilder's reticulum stain. $\times 250$.

7



8



Lucke

Recovery from Epidemic Hepatitis



SARCOIDOSIS OF THE SPLEEN

REPORT OF A CASE WITH AUTOPSY AND A STUDY OF INTRACELLULAR "ASTEROID BODIES" *

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Although Boeck's sarcoid of the spleen, as a more or less localized form of the disease, is described under that title in no previously published autopsy report, it undoubtedly is of occasional occurrence and should be included in the differential diagnosis of splenomegalies of obscure origin. In the literature there are several clinical case reports of splenomegaly caused by sarcoidosis, often unsuspected until discovered histologically, and it is probable that some autopsy reports of this disease have been published under another diagnosis, as I shall indicate later.

THE SPLEEN IN GENERAL SARCOIDOSIS

Involvement of the spleen in the course of generalized sarcoidosis is a fairly regular occurrence, as proved by both clinical and post-mortem data. Thus, Palmer¹ stated in his review, "of the abdominal signs, splenomegaly is the most prominent," and he added that slight splenic involvement is quite common and that occasionally the enlargement may be very great. Another example of this statement is found in the recent report of clinical data on five cases of Boeck's sarcoid, by Bernstein and Oppenheimer.² One spleen extended four fingersbreadth below the costal margin and had a palpable notch, a second spleen extended 2 cm. below the costal margin, a third extended 1 cm. below the costal margin, a fourth just reached the costal margin, and the fifth was not palpable. Of Nickerson's³ six patients, four had splenomegaly, with spleens weighing 200, 230, 640 and 890 gm. respectively. He stated that splenomegaly, with or without lymphadenopathy, was the most constant feature of his six cases.

Histologically, the spleen is the second most common site of involvement in generalized sarcoidosis, as shown in Table I. (The data have been collected from Pinner's⁴ review of all autopsied cases up to 1938 and from twelve subsequent case reports,⁵⁻¹² including my own. It is incomplete since in a few cases only partial autopsies were performed, while in others many tissues were not examined histologically. However, it provides a fairly correct picture of the relative incidence in the various tissues. The case of Ronchese¹³ and the sixth case of Bern-

* Received for publication, July 6, 1943.

stein and Oppenheimer² are not included in this anatomical summary because they show too much evidence of ordinary tuberculosis.) In view of the affinity of sarcoidosis for the reticulo-endothelial system, it is not at all surprising to find this high incidence in the spleen; nor is it surprising to observe that nearly all of the cases examined at autopsy show a widespread rather than a localized distribution of the disease, even though most of the patients had died of causes other than sarcoidosis itself.

TABLE I
*Incidence of Tissue and Organ Involvement in 29 Cases of Sarcoidosis
Examined by Autopsy*

Tissue or organ	Number of times involved
Lung	24
Spleen	21
Lymph nodes	21
Liver	17
Bone marrow	14
Skin	12
Kidney	7
Gastrointestinal tract	5
Trachea and bronchi	5
Tonsils	3

Other tissues reported to be involved 1 to 6 times are: heart, pituitary body, brain, spinal cord, meninges, prostate, testicle, epididymis, thyroid, pancreas, skeletal muscle and nasal mucosa.

OCCURRENCE OF LOCALIZED SARCOIDOSIS OF THE SPLEEN

In spite of this high incidence of splenic involvement in the generalized form, sarcoidosis of the spleen as a disease in its own right, with only insignificant or absent sarcoid lesions elsewhere, is but little known and therefore is usually unrecognized even when it does occur. The "pure" form, with no lesions outside of the spleen, is probably nonexistent, and the other cases with splenomegaly and vague symptoms predominant in the clinical picture have usually been misdiagnosed. Thus, Palmer¹ referred to enlarged spleens which were removed for "Banti's disease" and then found histologically to show sarcoidosis instead, and he therefore urged consideration of sarcoidosis in every case of chronic splenomegaly. In Jadassohn's¹⁴ third case, for example, the patient presented typical sarcoid lesions in skin and bones, responded negatively to the Pirquet and Mantoux (1:1000) tests for tuberculosis, and had had splenectomy for Banti's disease 3 years previously; the spleen showed sarcoidosis. In one of Longcope's⁹ cases of sarcoidosis, splenectomy was done for supposed Banti's disease and the diagnosis of sarcoid made after histological examination of the spleen. In Engelbreth-Holm's¹⁵ second case, in which splenectomy for supposed Banti's disease was performed, the patient responded nega-

tively to the Mantoux skin test for tuberculosis, showed no acid-fast bacilli in the spleen, and showed multiple, tiny, noncaseating tubercles in the spleen. Although the case is reported as tuberculosis of the spleen, this evidence is against tuberculosis and very strongly in favor of sarcoidosis, as will be discussed later.

Dressler's¹⁶ case of unexplained splenomegaly was diagnosed as sarcoidosis of the spleen on the basis of sarcoid lesions having been found in a sternal puncture, on roentgenological findings suggestive of hilar saroidosis, and on negative response to the Pirquet test and only weakly positive response to the Mantoux test (using 1 mg. of tuberculin). Dressler concluded that many cases diagnosed as Banti's disease or as tuberculous splenomegaly are actually sarcoidosis. That the possibility that sarcoidosis is a cause of splenomegaly of "obscure origin" is seeping into current clinical thought, is demonstrated by a recent clinicopathological discussion,¹⁷ involving a patient whose spleen reached nearly to his left iliac crest. His negative response to the Mantoux test for tuberculosis, the elevation of total serum protein, and the hyperglobulinemia were the only signs of sarcoidosis. This diagnosis was offered clinically, however, even before the pathologist's presentation, to the group, of sarcoid lesions in specimens of liver and eyelid removed for biopsy. (The spleen was not removed and the patient was living at the time of publication of that paper.)

TUBERCULOUS SPLENOMEGALY

"Primary" tuberculosis of the spleen, as opposed to the splenic lesions accompanying active tuberculosis elsewhere in the body, is accompanied by only minor tuberculous lesions elsewhere, usually in the abdominal lymph nodes, the liver and the lungs. As described by Winternitz,¹⁸ this is usually a severe and often fatal disease, and therefore I believe that patients with mild symptoms or with no symptoms at all should be regarded with suspicion until the diagnosis definitely has been proved. Many of the more recently reported cases have had such "peculiarities" as negative skin tests for tuberculosis, absence of tubercle bacilli in stained sections and even in inoculated guinea-pigs, absence of definite fever or of any severe symptoms, presence of only noncaseating tubercles, and evidence of active or healed "miliary tuberculosis" of the spleen with only mild symptoms and with recovery. It hardly need be stated that each of these items is a point in favor of sarcoidosis and against ordinary tuberculosis. In fact, a truly negative tuberculin skin test reaction in a patient with mild symptoms and noncaseating tubercles makes the diagnosis of sarcoidosis almost mandatory; and such occurrences as "healed miliary tuberculosis," or the

failure of tissue with *active* lesions to infect a guinea-pig, speak very strongly against tuberculosis but are the customary findings in sarcoidosis. Let us now examine some individual cases.

The earlier review by Winternitz¹⁸ contributes nothing definite to our search for cases of splenic sarcoidosis. The majority of his patients died as a direct result of splenic tuberculosis or its generalized dissemination, they had caseation in the splenic lesions, and undoubtedly were straight-forward cases of tuberculosis. Only a small number of his cases had miliary, noncaseous tubercles; a tuberculin test was reported in only one case (positive); and insufficient data are given to label any individual case even as "possible" sarcoidosis. Most of the cases mentioned by Lubarsch¹⁹ either had caseous tubercles or had insufficient data, but one of his cases is very suggestive of sarcoidosis. This patient had a chronic course with splenomegaly and lymphadenopathy, and the spleen was removed surgically and found to have small, miliary, pinhead-sized, noncaseating tubercles with a definite reticulum framework in each one. (This reticulum framework differentiates sarcoidosis from tuberculosis, according to Nickerson,³ and others.) A guinea-pig injected with splenic tissue from this patient was alive 2½ months later. To explain this apparently benign miliary tuberculosis, Lubarsch postulated a very low virulence for the tubercle bacilli in this case, which is one of the theories that have been offered for the explanation of sarcoidosis itself. (This patient is stated to have died of pulmonary tuberculosis some years later, after a healthy, asymptomatic interim; and although we might be tempted to consider the tuberculosis a separate disease in this case, perhaps even acquired during possible sanatorium treatment for his "tuberculous splenomegaly," nevertheless the mode of death forces us to doubt the classification of this case as Boeck's sarcoid.)

The report by Engelbreth-Holm¹⁵ of 28 cases of tuberculous splenomegaly subsequent to Winternitz's¹⁸ review presents rather hopeful material. His own second case (previously mentioned), with a negative response to the Mantoux test, was diagnosed clinically as Banti's disease and showed noncaseating tubercles and absence of tubercle bacilli in the surgically removed spleen; the patient was still living and well at the time of the report. His third case responded negatively to the Pirquet test for tuberculosis, had miliary noncaseating tubercles in the spleen, and showed a connective tissue framework in the tubercles. In his fourth case the spleen contained noncaseating tubercles and no acid-fast bacilli. Of the 28 cases he reviewed (including his own 4 cases), 3 had Pirquet tests done, and all three were negative. (All

were in cases with noncaseous tubercles.) Of the 9 cases reported as showing acid-fast bacilli in the tissue, 4 had miliary tubercles and 5 had larger caseous ones.

Since it would be unfair and inaccurate to use published statements and photographs to re-diagnose cases of other writers, I can offer no concise list of cases reported as tuberculous splenomegaly which should be labeled sarcoidosis; but I feel certain, for reasons already enumerated, that many such cases exist. The case presented herein is believed to be the first case of splenic sarcoidosis, with autopsy, to be reported under that diagnosis. The disease was asymptomatic, was accompanied by mild splenomegaly and with only a few, small, scattered, sarcoid lesions in other tissues, and was a purely incidental finding in a woman who had died of meningococcal meningitis. This case has also provided an unusual opportunity to study certain rather rare inclusion bodies which have been previously described in cases of sarcoidosis.

REPORT OF CASE

M. E. S. was a white woman, 63 years old, who had visited the medical outpatient department for sundry complaints during the past 5 years.

Past History. About 4 years previously her systolic blood pressure was reported to be 270 mm. of Hg by her family physician. A fairly complete study in the clinic 2 years previously had revealed complete heart block with a very slow pulse rate, evidence of aortic stenosis and very slight cardiac enlargement. At that time there was no enlargement of her lymph nodes. The total serum protein level was 6.7 gm. per 100 cc., and other chemical studies, blood counts, urinalyses, and the spinal fluid colloidal gold curve revealed nothing abnormal. Wassermann tests on blood and spinal fluid were negative. She had had weakness in the 6 months preceding her final entry, and had lost 10 pounds in weight in the past 2 months. Dyspnea had been gradually increasing during the past 2 years.

Present Illness. The patient was brought to the hospital in a semicomatose condition on January 4, 1943, and the history was obtained from her brother. She was said to have developed malaise and epigastric pain and to have vomited black material 2 days before entry. She improved on the following day, then suddenly became very ill, began to "scream with pain," became confused and glassy-eyed, and showed "red marks" on her chest.

Physical Examination. The patient was completely confused, showed rigidity of the neck and positive Kernig and Brudzinski signs, and had a macular petechial skin rash. Her eyes were fixed in a glassy stare. The blood pressure was 150 systolic and 80 diastolic, the pulse rate was 60 per minute, and there were systolic murmurs at the mitral and aortic valve areas.

Laboratory Findings. The white blood cell count was 24,000 per cmm. (about 90 per cent polymorphonuclear leukocytes), and the spinal fluid contained 2000 polymorphonuclear leukocytes per cmm., with intracellular and extracellular gram-negative diplococci.

Course. The patient rapidly became stuporous and died within 5 hours of entry.

Clinical Diagnoses. Meningococcal meningitis; chronic rheumatic endocarditis with aortic stenosis.

REPORT OF AUTOPSY

The autopsy was performed 14 hours after death.

Gross Findings

Skin. There were numerous small petechiae on the skin of the abdomen, the thorax and most of the flexor surfaces.

Heart. The heart weighed 500 gm. and showed thickened, fibrotic, partially calcified aortic valve cusps, which were partially fused and had caused marked stenosis of the valve. The mitral valve had thickened, fibrous, partly calcified leaflets and was slightly stenosed; the chordae tendinae were short and thick. The left ventricle was hypertrophied and measured 1.7 cm. in thickness.

Lungs. The lungs were congested and mildly edematous.

Spleen. The spleen weighed 300 gm., had a smooth red capsule, was slightly softened and showed on its cut surface a myriad of tiny white nodules 0.3 to 1.0 mm. in size, which were embedded in a soft red pulp. They could not always be distinguished grossly from malpighian corpuscles, although they were thought to be a trifle smaller and were discrete and circumscribed. No caseation nor large nodules were seen.

Lymph Nodes. No enlargement nor gross abnormality.

Liver. The liver was moderately congested. The *gallbladder* had a thin, tough, white, fibrosed wall and was completely filled by a large, rough, brown calculus.

Brain. The brain weighed 1360 gm. and had a moderately thick, diffuse, subarachnoid purulent exudate which was most abundant on the surface of the cerebral hemispheres.

Histological Findings

Spleen. The spleen was studded with discrete, circumscribed, tubercle-like lesions which were all of fairly uniform size (slightly smaller than a malpighian corpuscle) and located indiscriminately in the lymphoid tissue and sinusoidal areas. Although they sometimes overlapped, the lesions tended to retain their individuality rather than to become confluent. The individual lesion was elliptical or spherical, and had a smooth and sharply outlined border and a reticulum and collagenous connective tissue framework in which the fibers tended to radiate from center to periphery. There was a narrow zone of concentrically arranged reticulum fibers at the edge of each sarcoidal lesion. Endothelioid cells and multinucleated giant cells of various sizes were embedded in the pale-staining collagenous connective tissue, and these were sometimes oriented toward the center of the nodule.

In the larger giant cells there was a tendency for the nuclei to become bunched together at one end, while the cytoplasm forming the bulk of the cell became the site of certain striking processes. In most giant cells the cytoplasm showed a few or many punched-out clear areas, often with a tiny, pink-staining sphere or coccoid body in the center of each such vacuole. The larger vacuoles contained larger spheres, some of which had short, sharp pseudopodia or rays protruding from their surfaces. In other cells these rays had become much longer, additional rays appeared, and the structure increased in size until it reached the maximum size observed (about $25\ \mu$). At this stage there was rarely more than one such structure in any single cell, although many other "embryonic" vacuoles might be present, and the large parent vacuole had become very irregular in order to adapt itself to the shape of the full-sized body with its long rays. This fully developed star-shaped body, to which I shall refer as an asteroid, was somewhat more acidophilic and less granular than the cytoplasm of the giant cell and often had a small, bluish-pink-staining sphere exactly in its center. (The chemical properties are discussed later.) The asteroids were found nowhere except within the cytoplasm of multinucleated giant cells. Only about 6 or 8 per cent of giant cells had fully developed asteroids, although the majority of cells had small vacuoles. The accompanying high-power photomicrographs of various giant cells have been arranged in order of development to illustrate the hypothesis of growth just described.

No acid-fast bacilli were found in sections of spleen stained by the Ziehl-Neelsen technic.

Lymph Node. Section of a small abdominal lymph node near the gallbladder showed numerous, small, discrete collections of endothelioid and giant cells, with very little connective tissue and with no caseation in these lesions. These nodules were smaller and more youthful in appearance than those in the spleen, and their giant cells contained vacuoles and a few asteroids like those previously described.

Lungs. In several sections of lung tissue there was found an occasional, very tiny collection of endothelioid cells and perhaps a giant cell or two with an asteroid. There was some congestion.

Liver. In two large sections of liver there was found a tiny collection of cells similar to those in the lung. There was moderate passive congestion.

Brain. There was some edema of the molecular layer of the cerebral cortex, adjacent to the thick layer of subarachnoid polymorphonuclear exudate.

Other Tissues. Sections of myocardium, pancreas, gallbladder,

adrenal, kidney, ovary, pituitary gland, and abdominal skin showed no evidence of sarcoidosis, nor of any other lesion except chronic cholecystitis. Other tissues were not sectioned.

Unfortunately all of the tissues were placed immediately in fixative and nothing was available for culture or animal inoculation, as the presence of sarcoidosis was not suspected until the slides were seen.

Anatomical Diagnoses

Meningococcal meningitis; rheumatic endocarditis, mitral and aortic, with aortic stenosis and left ventricular hypertrophy and with passive congestion of lungs and liver; chronic cholelithiasis and cholecystitis; sarcoidosis of the spleen and lymph node, with isolated tiny sarcoidal lesions in the lungs and liver.

STAINING AND CHEMICAL REACTIONS OF ASTEROIDS

Since the asteroids were found only within giant cells of the specific lesions in spleen, lymph node and lung; since I have not seen them in tuberculous or other material treated with the same formaldehyde fixative; since they are present in frozen sections as well as in paraffin sections; and since they are seen with all stains and even in unstained sections, they are presumed *not* to be artifacts and to be definitely part of the sarcoidal lesion. A resumé of their properties, as thus far determined, is as follows:

1. Solubility. Asteroids fail to dissolve in water, alcohol, or xylol.
2. Hydrogen ion concentration. The asteroids neither dissolve nor show any morphological alteration when sections of spleen 5 μ in thickness are immersed in either 1 per cent sodium hydroxide or 10 per cent formic acid for 15 minutes.
3. Fat stains. With scarlet red or Sudan III the asteroids remain unstained; some macrophages and a few giant cells contain small globules of neutral fat, but no fat is found in the specific vacuoles of the giant cells. With Nile blue sulfate asteroids are dark blue. With Fischler's fatty acid stain asteroids are very faintly salmon colored (negative).
4. Hematoxylin and eosin. Asteroids are pink.
5. Phosphotungstic acid hematoxylin. Asteroids are vaguely bluish or sometimes pale orange.
6. Mallory's connective tissue stain. Asteroids are reddish violet (about the same as cytoplasm of cells), negative for collagen.
7. Masson's trichrome stain. Asteroids are gray (negative for collagen).

8. Hematoxylin and van Gieson's stain. Asteroids are yellow (negative for collagen).

9. Wilder's reticulum and van Gieson's stains. Asteroids are pale pinkish yellow (negative for reticulum).

10. Weigert's elastic tissue stain. Asteroids contain no elastic tissue (nor does the rest of the sarcoidal lesion).

Conclusion. The asteroids are relatively stable chemically; they respond negatively to the more common stains for specific substances, and they exhibit approximately the same staining reactions as the cytoplasm of endothelioid or giant cells.

DISCUSSION

Such asteroids have been known for some time in connection with sarcoidosis, and Jadassohn,¹⁴ in 1919, referred to "asteroid bodies" of unknown microchemical identity in his first case. They are rarely mentioned in the more recent literature on sarcoidosis, however, probably because they occur infrequently (judging by the other sarcoid material in this laboratory).

A type of inclusion body which was not found in this case but which is commonly described in sarcoidosis and which has been exhaustively studied by Schaumann²⁰ is roughly spherical or oval-shaped, often has concentric laminations, may show yeast-like budding, is nearly always calcified, and is usually large and often much larger than its parent giant cell. Some of these bodies show rays or fascicles, suggesting that they may be an older, more chronic, calcifying stage of the asteroid. Schaumann contended that these calcifying bodies may represent tissue reaction around nonbacillary, fungoid or mycotic forms of the tubercle bacillus, and that this nonbacillary form of the organism may be the etiological agent of sarcoidosis. Although the asteroid may possibly be a less mature form of the calcifying inclusion body, I can offer no evidence from this case to prove any relation between the asteroid and the tubercle bacillus (nor any evidence against such relationship).

Wolbach,²¹ in 1911, described intracellular bodies exactly similar in morphology and most staining reactions to these asteroids. These were found in 5 cases in a series of 900 autopsies. The patients had died of such diverse diseases as malignant neoplasms and pernicious anemia, and following thyroidectomy. He therefore concluded that these bodies were nonspecific. This study was completed before the general recognition of Boeck's sarcoid as a disease entity, and Wolbach's description of these bodies in noncaseating "tubercles" which tended to undergo fibrosis is very strongly suggestive of sarcoidal lesions; his painstaking

care to rule out tuberculosis as the cause of the tubercles is further evidence of this point. The diversity of the principal diseases in the 5 patients detracts nothing from the possibility of their having sarcoidosis, as most of the published autopsy reports of cases of sarcoidosis state that some other disease was the cause of death. An interesting point is the combined distribution of lesions in Wolbach's 5 cases (lung, lymph nodes, liver, spleen), which is precisely the distribution in my single case.

Wolbach's²¹ conclusions that the asteroid body is nonspecific, is not a parasitic organism and is a biochemical alteration of cytoplasm might be modified in the light of present knowledge to the following:

1. The asteroid *may* be nonspecific but is characteristically found in sarcoid lesions.
2. The possibility of its being an extraneous organism cannot be excluded, although it is doubtful.
3. Its causation and its chemical or histological identity are still unknown, specific tissue stains give negative results and it does not exhibit the features of a crystalline body.

SUMMARY

1. Sarcoidosis of the spleen is an occasional clinical condition which should be considered in cases of obscure splenomegaly. In the past it has been misdiagnosed most often as Banti's disease or as tuberculous splenomegaly.

2. In the case presented, sarcoidosis was found at autopsy to be primarily splenic. In this instance sarcoidosis was asymptomatic and was an incidental finding in a patient who died of meningococcal meningitis.

3. Intracellular asteroid bodies were present in the sarcoidal lesions. Investigation by histochemical methods failed to give definite information as to their causation or histological identity.

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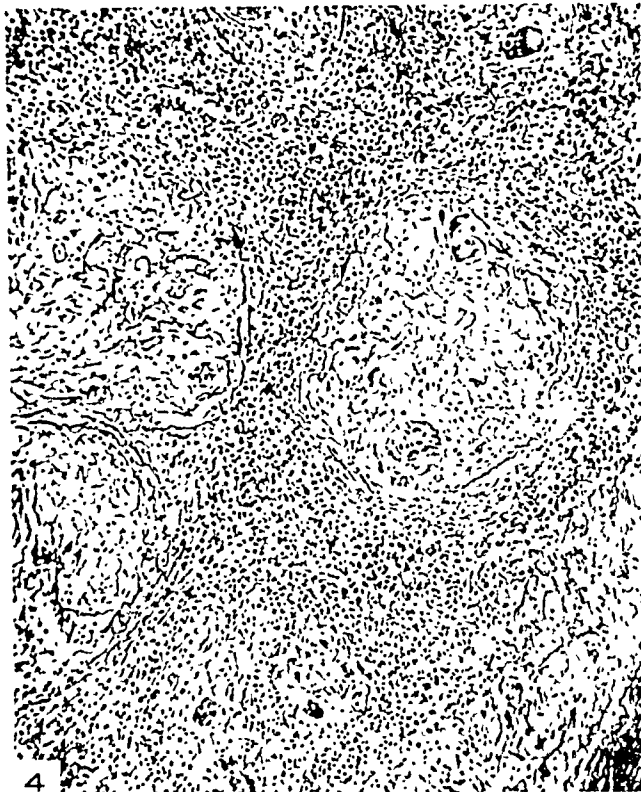
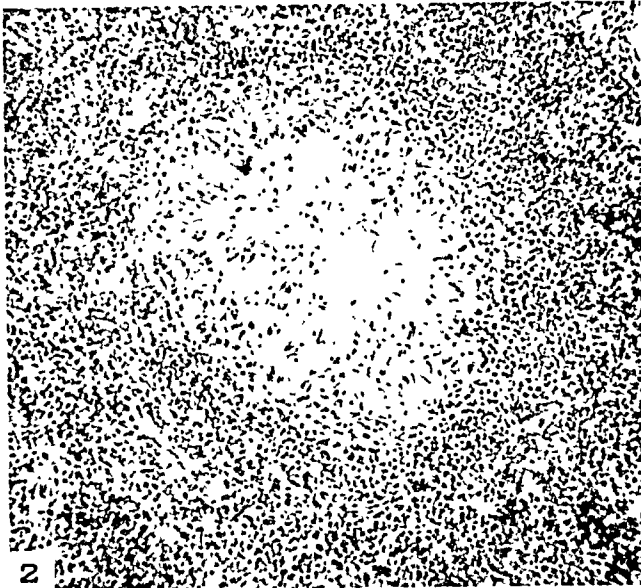
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[Illustrations follow]

DESCRIPTION OF PLATES

PLATE 125

- FIG. 1. Sarcoid nodules in spleen, showing smooth, sharp borders. Hematoxylin and eosin stain. $\times 30$.
- FIG. 2. Single nodule in spleen, showing one giant cell and much fibrosis. Hematoxylin and eosin stain. $\times 90$.
- FIG. 3. Typical, but relatively insignificant, collection of a few giant and endothelioid cells in lung. Hematoxylin and eosin stain. $\times 90$.
- FIG. 4. Reticulum framework of sarcoid nodules in spleen. Wilder's reticulum stain. $\times 90$.



Friedman

Sarcoidosis of the Spleen

PLATE 126

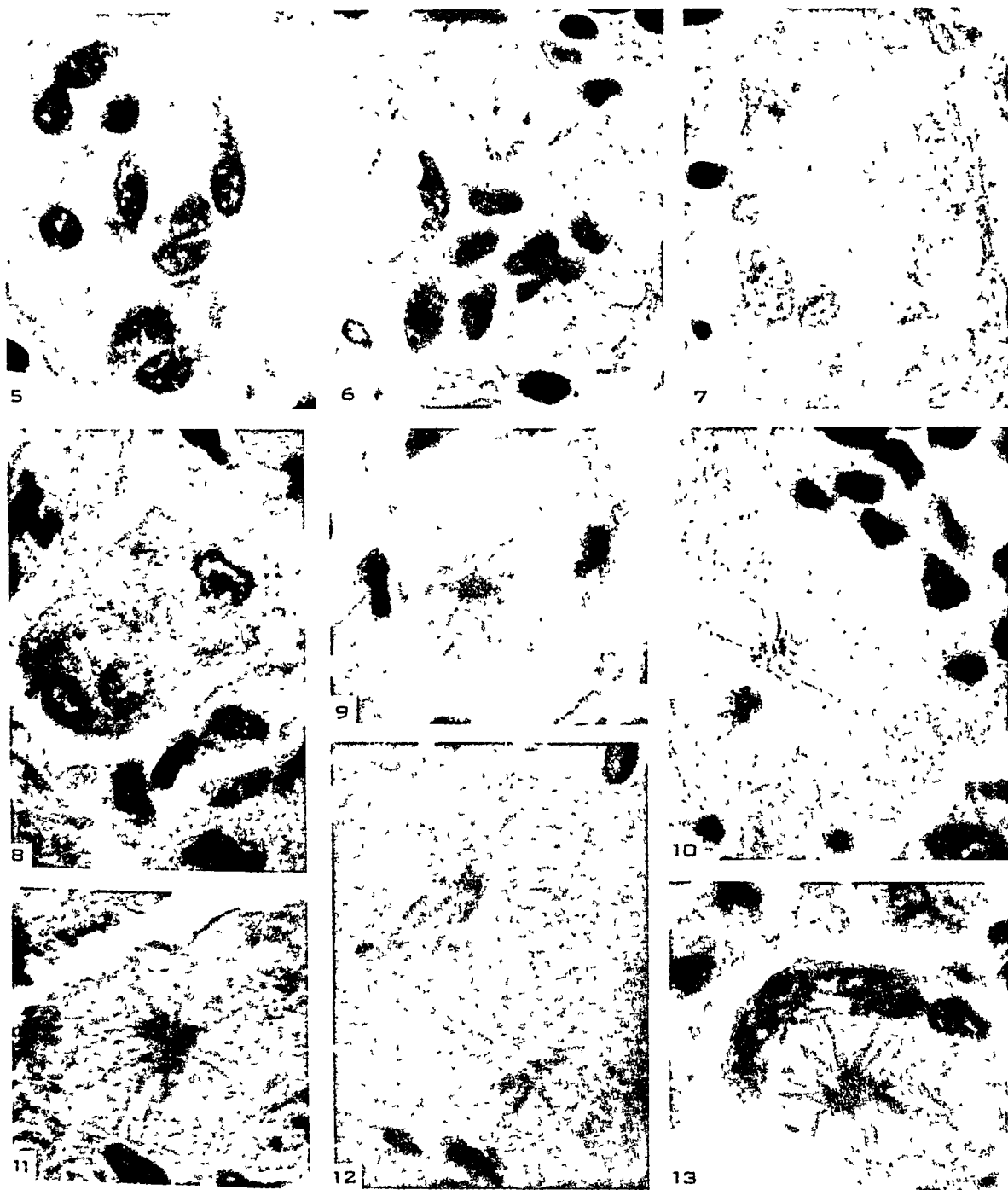
(All figures are from the spleen)

FIG. 5. Giant cell with early vacuole formation. Hematoxylin and eosin stain. $\times 795$.

FIGS. 6 and 7. Several coccoid bodies have tiny irregular spicules. Hematoxylin and eosin stain. $\times 795$.

FIGS. 8, 9 and 10. Asteroids of intermediate size; numerous coccoid bodies are present in small vacuoles in Figure 10. Hematoxylin and eosin stain. $\times 795$.

FIGS. 11, 12 and 13. "Fully developed" asteroid bodies in giant cells. Hematoxylin and eosin stain. $\times 795$.



Friedman

Sarcoidosis of the Spleen

HISTOLOGY OF CEREBRAL LESIONS PRODUCED BY FOCUSED ULTRASOUND*

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Ultrasonic waves, sometimes called supersonic waves, are mechanical or elastic vibrations in any solid, liquid, or gaseous medium of a frequency above the range of audible sound, namely, above 16,000 cycles per second. Although the physical laws of audible sound also apply in the higher supersonic frequencies, the latter exhibit additional phenomena not found in the audible range. These special phenomena are a result of the high frequency and short wave length. Ultrasonic waves are, for example, capable of producing destructive changes in living tissue. Some of these changes are: mechanical "trip hammer-like" beating with rupture of the tissues, heat generation and sudden explosive liberation of dissolved gases from solution in the irradiated tissues with a resulting cavitation which resembles a localized caisson disease. Finally, ultrasound has the property of being focusable within a small spot a few millimeters in diameter. This property of focusability, in conjunction with the special tissue effects, suggests the possibility that an optimum combination of wave length, intensity and exposure might be found which would produce a focal destruction in the depths of tissues, without injuring the intervening layer. While this possibility has not been realized in the present experiments, it has been approached.

Since Harvey, Harvey and Loomis,¹ in 1928, conducted their pioneering experiments on the biological effects of ultrasound on living microorganisms and animals, a host of domestic and foreign workers have extended its biological and industrial applications. At frequencies above 500 kilocycles, the supersonic waves are produced by driving a quartz crystal to expand and contract along its x-axis with an alternating current which is tuned to the same frequency as the natural frequency of the crystal.

In 1935 the physicist, Gruetzmacher,² ground the surfaces of a vibrating quartz plate so that they had a curve similar to that of a concave mirror. This caused the ultrasound waves thrown off to converge and come to a focus. In so far as we are aware, the present series of

* This report was presented in condensed form under the title of "The Use of Focused Ultrasound Waves for the Production of Transcranial Focal Brain Lesions: a Preliminary Report" before a combined meeting of the New York Neurological Society and the Section on Neurology and Psychiatry of the New York Academy of Medicine, December 8, 1942.

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studies represents the first biological applications of this new curved quartz plate method of obtaining local concentrations of ultrasonic energy. In the experiments herein reported we have used a quartz plate generator with the following specifications: round, diameter 5.08 cm., frequency 835 kc., curved to focus at a spot 5.5 cm. from the concave crystal surface or 4 cm. above the center of the flat cellophane diaphragm. The focal spot in water has the same diameter as the wave length, namely, 1.8 mm. Technical details regarding the construction and operation of both the radio-frequency and the focusing ultrasound generators have already been reported.³

MATERIAL AND PROCEDURES

In all, 3 dogs, 30 cats and 4 monkeys were used. The animals were all under ether anesthesia. Various areas of their heads or backs over the spinal column were shaved free of hair and then placed against the cellophane diaphragm of the focusing ultrasound generator in the manner seen in Figure 1. An ultrasound transmission medium of a few millimeters of olive oil always had to be used between the skin and the diaphragm, taking care that no bubbles of air were present anywhere between the source of ultrasound and the skin surface, since the presence of air bubbles absorbs and disperses the radiations.

All except the last of the 37 experimental animals were treated from 5 to 15 minutes with maximum doses of focused ultrasound. Our overcautious attitude towards the danger of breaking the quartz caused us routinely to increase very slowly the voltage applied to the crystal generator. It usually took 30 to 60 seconds for the intensity of the striking force of the focused ultrasound to be increased from 0 to peak output, at which level it could be maintained with safety for the crystal during the remainder of the treatment period.

BEHAVIOR AND STRUCTURAL CHANGES FOLLOWING APPLICATION OF FOCUSED ULTRASOUND TO THE NERVOUS SYSTEM

The most characteristic deviations in behavior which were produced were blindness after transcranial irradiation of the striate region of the occipital cortex, ipsilateral incoordinations and ataxia from an application to one cerebellar lobe, bilateral paralysis and anesthesia of the hind extremities following treatment of the lumbar cord region, and monoparesis of the right forelimb after irradiation of the forelimb area of the contralateral motor cortex.

Immediately after a treatment of 3 minutes or longer at maximum intensity the skin had a slightly yellowish tinge, probably due to the contact medium of olive oil having been driven into the pores by the

radiation pressure. Swelling and edema of the skin and underlying soft tissues did not become manifest for 10 or 15 minutes and then persisted for 3 or 4 days, during which time the skin gradually turned a brownish gray. By the end of 8 or 9 days the edema had disappeared but the skin was dead and leathery in consistency and appearance. It was sharply demarcated from the healthy skin by an inflamed margin from which it could be detached. By this time, the underlying soft tissues and muscles were markedly blanched, cold, and free from any signs of circulation or edema. In fact, they were even shrunken and atrophic, and the muscle cells showed disappearance of their nuclei and fading of cellular outlines. The round area of necrotic muscle was as sharply demarcated from healthy muscle as was the treated area of overlying skin from the healthy skin.

By the end of 12 days, the affected area presented the typical depressed, shrivelled and hornified appearance of dry gangrene (Fig. 2). Except for a slight yellowish discoloration of the periosteum, the skull and vertebrae showed no signs of injury. This was also true of the dura mater, except in two animals which exhibited epidural and subdural hemorrhages respectively. The nervous system always seemed to be damaged when the thinness of the overlying superficial soft tissues permitted the transmission of a sufficient concentration of the ultrasonic radiations. The character and location of this neural damage will be described in the representative protocols of experimental animals. These protocols include descriptions of the abnormalities of behavior produced in association with specific neural lesions. All animals, with the exception of monkey 4, were killed for autopsy by injecting 30 to 40 cc. of an 8 per cent solution of formaldehyde into the heart. After gross pathological changes had been noted, the brains and cords were fixed in a 4 per cent solution of formaldehyde, imbedded in paraffin and sectioned and stained by Nissl and silver impregnations.

Four animals will be described briefly as representative of the 37 animals used in this series. They give ample evidence of the functional and structural changes produced in the nervous system by focused ultrasound.

Cat 56: Transcranial Application to Occipital Striate Area

The cat became totally blind with recovery 4 hours later. Autopsy at this time showed edema and inflammation of cortico-striate regions on both occipital lobes.

The animal was a healthy male cat, weighing 4.1 Kg. After the routine preparations the occipital midline region of the head was placed against the diaphragm of the ultrasonic generator. The cat was given a 15 minute treatment at peak ultrasonic output level (radio-frequency current, 0.85 amperes).

One hour after treatment the animal was completely out of the ether anesthesia. The scalp was edematous over the area treated. He crawled slowly about the floor with perfect coordination but with his nose and belly touching the ground. He bumped his nose repeatedly against the walls and furniture. This invariably produced an immediate rapid backward withdrawal followed by a change in the direction of his creeping progress. Waving a hand in front of his eyes, or flashing a light into them, produced no distraction of attention and no change from the progressive belly crawling and nose-down position. Both pupils contracted equally to light. Clapping of the hands or ringing a bell caused pricking up of the ears and a momentary swinging of the head in the direction of the sound.

Four hours after exposure to ultrasound the cat walked normally, erect, avoiding with ease all objects in his path. The only behavioristic deviation observed at this time was a marked photophobia. Flashing a light into his eyes produced many meows in association with a precipitous flight to a shady corner.

Pathological Findings. Four and one-half hours after treatment the animal was killed and autopsied in the standard manner. The scalp showed the usual area of severe damage which appeared as a round, darkened, edematous patch about the size of a twenty-five cent piece. A trephine opening was made through the skull in this region, and the brain and meninges tended to bulge outward through it. They showed dilated blood vessels. The underlying occipital cortex for about 1 cm. bordering both sides of the posterior one-third of the longitudinal sulcus was moderately edematous with an ironing out of convolutions and sulci. The remainder of the brain and meninges appeared normal.

Monkey 2: Transcranial Application to Arm Area of Right Motor and Premotor Cortex

This monkey had a persistent spastic paresis of the left upper extremity which underwent only a partial recovery after 12 days, at which time autopsy showed a well circumscribed focal lesion in the right motor and premotor cortical arm area.

Monkey 2 was a healthy male animal which, after the usual preparations, was given a 10 minute dose of focused ultrasound at maximum intensity to the head over the right motor and premotor cortical arm areas.

One hour after treatment, he was completely out of anesthesia, leaping and climbing about carrying his left upper extremity in a semiflexed spastic position (Figs. 3 and 4). He succeeded in using it only very little, mostly at the shoulder and elbow when climbing and eating. Grasping of food and objects was done largely with the right hand. The left hand pushed slightly but could not grasp. The left arm muscles were spastic, with hyperactive deep reflexes. He could not support his weight with his left hand and arm.

Twelve days after ultrasonic application, the animal showed a typical dry gangrene of the soft tissues of the scalp overlying the region irradiated (Fig. 2). However, there was a return of much of the use of the left hand and arm, as shown by greater use in eating and climbing, with improved grasping and weight-supporting ability. Despite this improvement there was still an obvious residual paresis associated with manual clumsiness, a hyper-reflexia, and tendency to carry the member in a semiflexed position.

Pathological Findings. On the afternoon of the 12th day after treatment, the animal was killed and autopsied according to the usual procedure. Grossly the brain exhibited areas of old pial hemorrhagic discoloration over the middle portion of the right motor and premotor cortical regions. These even extended into the adjacent frontal and post-central areas (Fig. 5). Microscopically, this region

showed the usual clearly defined cone-shaped region of necrosis with the base at the surface of the cortex. On cross section the necrotic area appeared triangular (Fig. 6), and was walled off from the normal cortical tissue by a heavy layer of glial and blood vessel proliferation. In the severely affected region there were barren acellular areas where only an occasional ganglion cell remained. These showed swollen, tortuous, broken or missing processes. Figure 7 illustrates such a nerve cell with its apical dendrite swollen and corkscrew-shaped.

Cat 153: Transcranial Application to Left Cerebellum

The cat exhibited a marked ataxia, incoordination and weakness of his left hind extremity, without, however, any sensory disturbance. This lasted over an hour and was followed by an apparent complete functional recovery, despite subsequent morphological evidence of persistent damage to the ganglion cells of the left cerebellar cortex.

Cat 153 was a healthy male animal, weighing 3.8 Kg. After the usual preparations the left cerebellar region was given 15 minutes of irradiation at maximum intensity.

One hour afterwards the animal was completely recovered from the ether anesthesia but walked with hind legs forming a wide base. The skin and soft tissues over the cerebellar region treated were darkened and edematous. The left rear extremity was weak, unsteady and ataxic when walking. Stepping on the animal's tail directly posterior to its body as it lay on the floor caused a violent struggle to escape, with marked deviations to the left on each of eight trials. Alternate pinpricking of right and left fore-shoulders produced successful avertive movements to the left only, in all of ten trials. When the animal was dropped from a height of 4 feet, the left hind extremity collapsed and precipitated the cat to the floor.

Two hours after the ultrasonic treatment the animal was completely recovered with no signs of ataxia or weakness. On falling, it landed normally on all four legs.

Pathological Findings. Two days after treatment the cat was killed and autopsied in the usual manner. The skin and soft tissues at the site of treatment were beginning to undergo necrosis. A small area the size of a dime on the surface of the left cerebellar hemisphere appeared "moth-eaten." Microscopical examination showed a cone-shaped region of massive destruction of cerebellar tissue lying below this surface area. Adjacent regions of the cerebellum showed no damage (Fig. 8).

Monkey 4: Transcranial Application to Left Cerebellum with Sudden Death

Contrary to the usual practice, *instantaneous* full power of focused ultrasound was applied over the left cerebellum of monkey 4. The animal died within 45 seconds.

The animal was a healthy male. He was placed with his shaved left cerebellar region over the ultrasound generator. The full current of 0.76 amperes was applied *instantaneously* to the crystal with the production of an equally sudden peak intensity of application of the focused ultrasonic radiations to the monkey's left cerebellum and brain stem. Within 10 seconds, the animal was breathing irregularly and in 45 seconds his breathing had ceased. At this time the ultrasound was turned off. All attempts at resuscitation were useless. The quartz crystal was found to have been fractured. An autopsy was done immediately.

Pathological Findings. A small, round, slightly "moth-eaten" area was present on the surface of the left cerebellar hemisphere. The overlying skin and superficial tissues appeared normal. A microscopical study of the cerebellum showed a well

defined and well localized cone-shaped region about 1 cm. across the base and extending about a centimeter below the surface of the left cerebellar cortex. This region exhibited acute edema with cavitation and dismemberment of the neuro-architecture. This was especially evident in the molecular layer. The Purkinje cells were distorted and swollen (Fig. 9). The remainder of the cerebellum and brain stem seemed normal. No structural changes were visible which could account for the sudden death of the animal.

DISCUSSION OF FINDINGS

As can be seen in the sample animal protocols presented herein, all circumscribed *in vivo* neural lesions produced to date, with the exception of one, have been associated with a severe necrosis of the adjacent scalp and skin areas lying in the path of the ultrasound radiations, although there was no detectable damage to the bone and meninges. It was felt that sufficiently circumscribed brain and cord lesions had been produced transcranially and transvertebrally to justify this early report.

In contrast to the cats and dogs, the monkeys were especially satisfactory experimental animals because of the almost complete lack of radiation-absorbing muscle tissue over the skull areas adjacent to the motor and occipital regions of the cortex, and because of the greater degree of corticalization of function which resulted in the production of more clear-cut and more persistent focal disabilities.

In general, it can be said that the initial effect of focused ultrasound irradiation of maximum intensity, *instantaneously* applied, is characterized by a mechanical tearing of the tissue architecture and the formation of cavities which may or may not be due in part or in whole to the sudden explosive release of dissolved gases from tissue solution, "le phénomène de cavitation,"⁴ (Fig. 9). Rapid development of edema with dilatation of capillaries follows immediately. The most vulnerable cells are the ganglion cells. They show the greatest degree of destruction and reaction of degeneration (Figs. 6 and 7). The second most vulnerable structures are the glial cells which, if not destroyed along with the neural elements, are usually stimulated to diffuse proliferative overgrowth (Figs. 6 and 7). The least affected of all the cerebral tissues are the blood vessels, which usually show damage in the regions of tissue interfaces only, such as on the surface of the brain or dura mater. At these sites ruptured capillaries with areas of petechial hemorrhage are sometimes observed (Fig. 5). Within the nervous system *per se* the blood vessels may occasionally exhibit damage, but are usually stimulated so that subsequent capillary proliferation and endothelial thickening are seen throughout parts of treated areas of the brain and cord (Figs. 6 and 7).

SUMMARY AND CONCLUSIONS

A new method of producing transcranial and transvertebral focal lesions of the nervous system with a focused beam of ultrasound has been developed and employed with partial success in experiments with 37 cats, dogs and monkeys. At the will of the operator, reversible, partially reversible and irreversible disabilities could be produced. Some of these were cortical blindness, cerebellar ataxia, monoparesis, and bilateral paresis of the hind extremities. The central lesion generated, and directly responsible for a disability, was uniformly a roughly cone-shaped area 1 or 2 cm. across at the base and extending about the same depth below the surface of the brain or cord. All surrounding neural tissues were normal. The order of decreasing vulnerability to focused ultrasound of the cerebral or cord structures lying within such a cone-shaped lesion was found to be neuron cells, glia and blood vessels. However, in all experimental animals to date, with one important exception, there was always found associated with the central neural lesion a severe peripheral injury to the skin and soft tissues overlying the brain or cord areas treated.

We wish to acknowledge with thanks the aid of Miss Rosette Spoerri of the Department of Anatomy, College of Physicians and Surgeons, Columbia University, who prepared the histological material.

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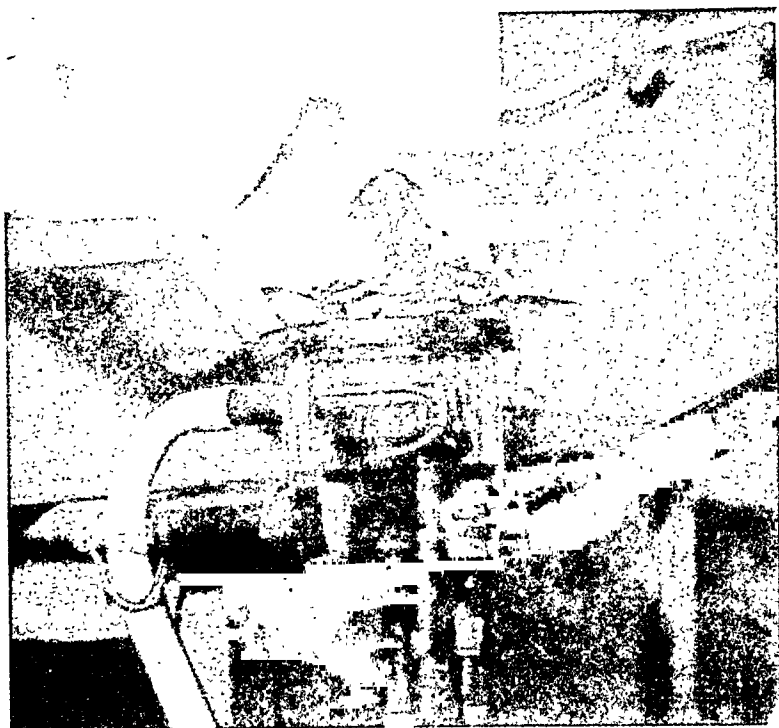
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[Illustrations follow]

DESCRIPTION OF PLATES

PLATE 127

- FIG. 1. The ultrasonic generator in operation with a cat's head in position for irradiation of the left cerebellar region.
- FIG. 2. Dry gangrene of soft tissues of scalp on monkey 2, 12 days after a 10 minute exposure to intense focused ultrasound.
- FIGS. 3 and 4. Two views of a left spastic monoparesis in monkey 2, 1 hour after a 10 minute transcranial application of focused ultrasound to the right motor and premotor areas.
- FIG. 5. An area of subpial petechial hemorrhage on the cortical surface outlines the boundary of the right premotor and motor regions treated. This resulted in the production of the left monoparesis seen in monkey 2, Figures 3 and 4.



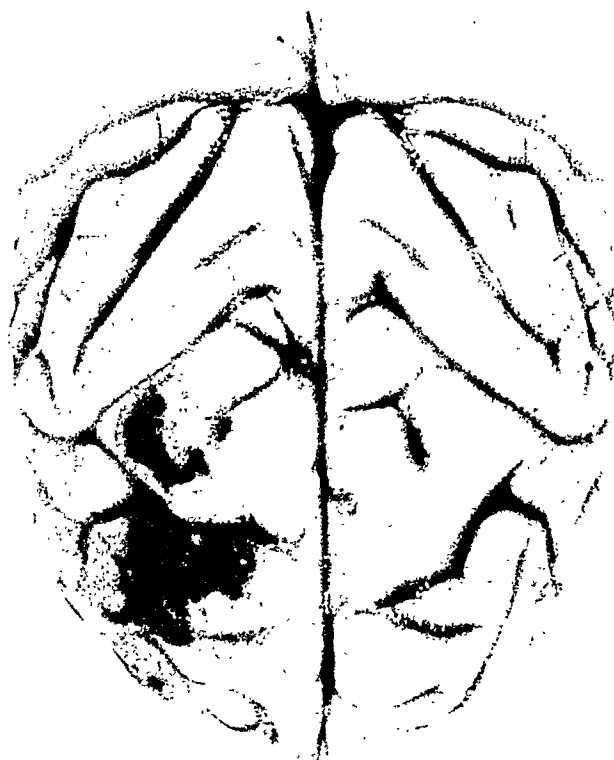
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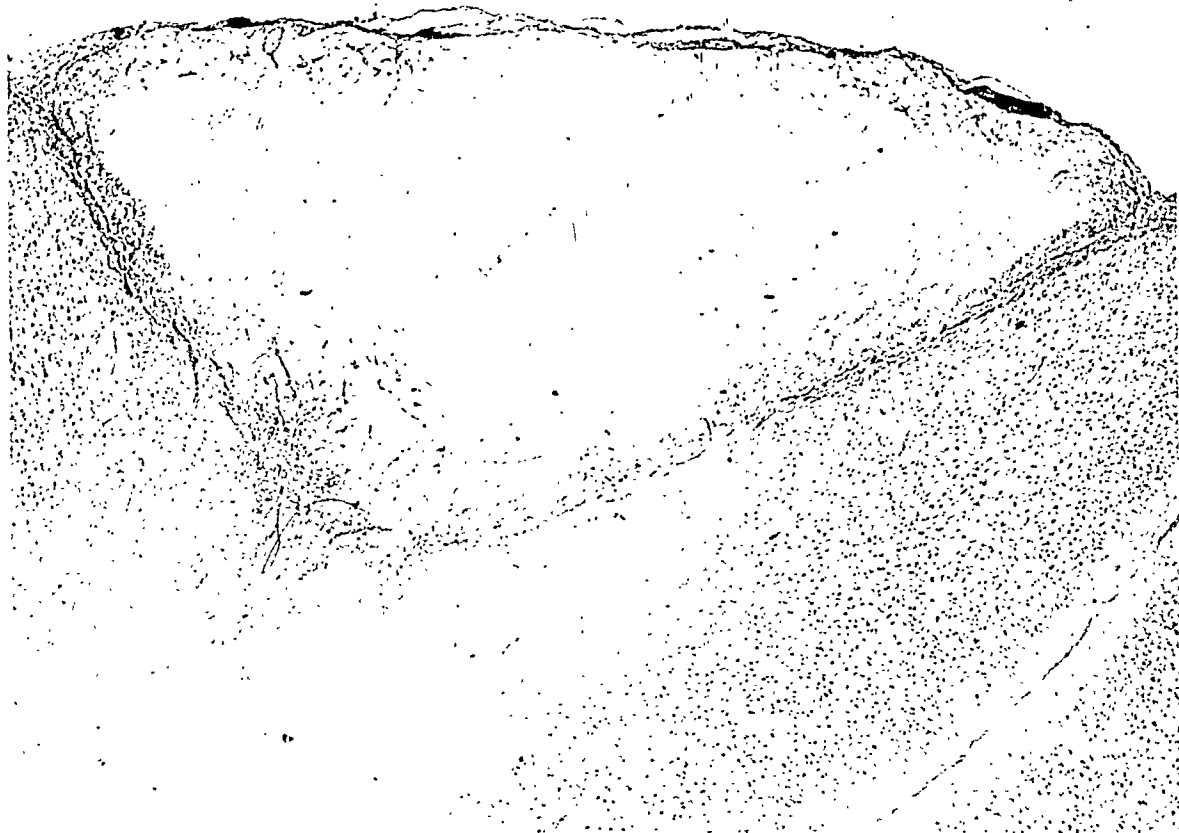
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PLATE 128

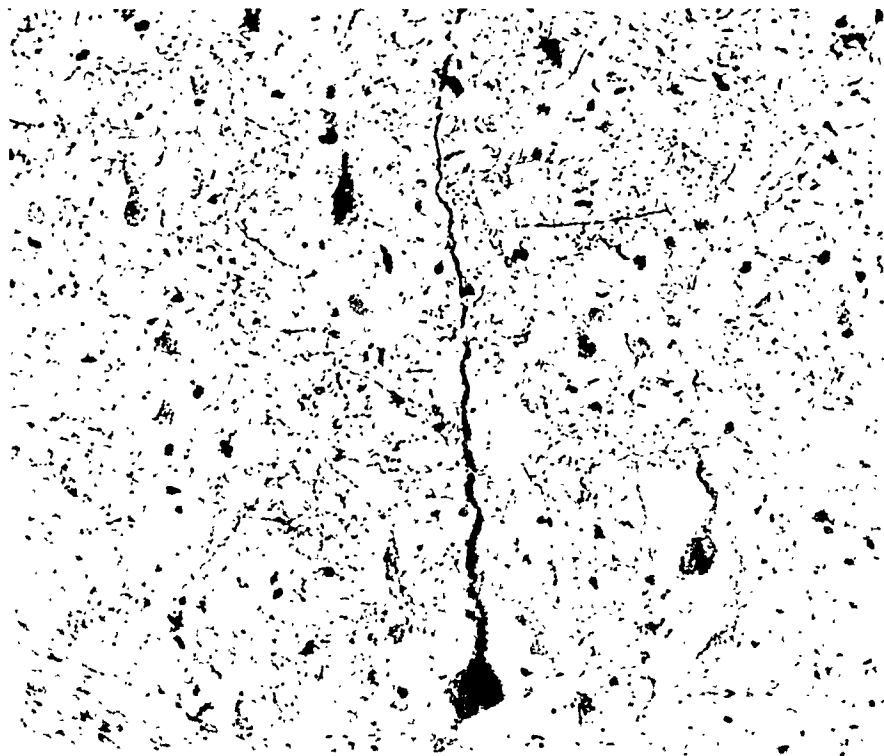
FIG. 6. Cross section of motor and premotor cortical area of monkey 2. Surface view is shown in Figure 5. The usual cone-shaped region of necrosis is present 12 days after treatment with focused ultrasound. This region is relatively barren and acellular with only occasional atypical ganglion cells remaining. The severely affected region has been walled off from the normal cortical tissue by a zone of glial and vascular proliferation. Modified Nissl's stain. $\times 50$.

FIG. 7. High-power study near the margin of the necrotic region shown in Figure 6. Ganglion cells are scarce and show thickened, broken, tortuous and even missing processes. One large ganglion cell has a swollen and corkscrew-shaped apical dendrite. Silver modification. $\times 235$.

6



7



Lynn and Putnam

Lesions Produced by Focused Ultrasound

PLATE 129

FIG. 8. Left cerebellum of cat 153, 2 days after 15 minutes of transcranial application of focused ultrasound at maximum intensity. There is a well localized region of massive destruction of tissue near the surface of the hemisphere. Adjacent areas show no damage. Modified Nissl's stain. $\times 35$.

FIG. 9. Leaflet of left cerebellum of monkey 4 immediately after 45 seconds of focused ultrasound was applied transcranially and instantaneously at maximum intensity. Molecular layer is most affected. The tissue has been torn and disrupted, leaving irregular gaps. In addition, diffuse edema exists throughout this layer, while the Purkinje cells show acute distortion and swelling. Silver modification. $\times 85$.



Lynn and Putnam

Lesions Produced by Focused Ultrasound

STUDIES ON THE HEMORRHAGIC AGENT
3,3'-METHYLENEBIS (4-HYDROXYCOUMARIN)

IV. THE PATHOLOGIC FINDINGS AFTER THE ADMINISTRATION
OF DICUMAROL *

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School, Madison, Wis.)

It has now been established by many investigators that the administration of Dicumarol to animals and human beings causes a decrease in the prothrombin of blood. This decrease is roughly proportional to the dosage, and death, with or without bleeding, may result from the administration of excessive quantities. Since prothrombin is produced mainly, if not entirely, by the liver, it is a matter of concern whether the liver is damaged by the exhibition of Dicumarol. Before administering the drug to human beings, therefore, we gave it in large doses to 25 dogs at the outset, and subsequently to 4 more. To several of these 29 animals fatal doses were purposely administered. Recently 6 other dogs received Dicumarol in doses approximating those that are now being administered to human beings. It is the purpose of this communication to record our gross and microscopic pathologic findings.

In the early studies on the fatal cases of hemorrhagic sweet clover disease in cattle Schofield¹ reported that gross lobular lesions had been found in the liver. Roderick,² however, observed only areas of focal necrosis and these in only half of his cases. He believed that the lesions described by Schofield were due to post-mortem changes. We³ have previously reported the absence of significant changes in the liver of any dog. Rose, Harris and Chen,⁴ however, who have administered large single doses of the disodium salt of Dicumarol to mice, rats and guinea-pigs, and large daily doses for prolonged periods to dogs, rabbits, mice and rats, found central necrosis of the liver in about half the rats examined post-mortem, and occasionally in rabbits, mice and dogs. The rat's liver appeared to be definitely more susceptible to Dicumarol than that of other animals. Five of the 21 dogs that were killed with daily doses of 5 to 50 mg. per Kg. showed central necrosis microscopically, moderate in 1 and slight in the remaining 4.

PROCEDURE AND RESULTS

The first 25 dogs received a wide range of dosage: 9 received sublethal oral doses and were killed by shooting, by injection of air or a

* This investigation has been aided by a grant from the Wisconsin Alumni Research Foundation.

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barbiturate into the jugular vein, or by operation with blood loss; 6 received single doses of 35 to 50 mg. per Kg. of the disodium salt of Dicumarol intravenously, and all died without gross evidence of hemorrhage; 2 received single doses of 5 gm. orally, and the remaining 8 received repeated smaller but cumulatively fatal doses over periods up to 7 days. In one instance the total quantity administered in a series of oral doses was greater than 5 gm.

The last 4 dogs of the original 29 were given Dicumarol after we had visited Mr. Rose and Drs. Harris and Chen in Indianapolis in January, 1942, at which time these workers kindly made available their data and animal tissues for study. In these 4 dogs only did we approach the intensive therapy with Dicumarol used by Rose, Harris and Chen,⁴ the dosage being 10 mg. per Kg. daily. On this regime 1 dog died on the 8th day after treatment was begun, 1 on the 12th day and 2 on the 14th day.

In none of these 29 dogs, whether given sublethal or lethal doses, was central necrosis of the liver demonstrated. In the animals given large single oral or intravenous doses, death occurred in 3 or 4 to 24 hours without evidence of hemorrhage. Some, but not all, of the animals given sublethal doses showed evidence of hemorrhage at various sites, including the lungs, pleura, gut, and the subcutaneous and intramuscular tissues. In virtually all those that died with hemorrhage, and in many that received sublethal doses of Dicumarol, widespread dilatation of capillaries, arterioles and venules, with degenerative changes, was noted. In the last 4 of the 29 dogs the conditions of administration of the drug were similar to those of Rose, Harris and Chen.⁴ Since there were only 4 animals, and since 16 of the 21 studied by Rose *et al.* showed no liver change either, it is obvious that chance alone might account for the fact that we did not make identical observations.

Since no one would deliberately give so large a dose as 10 mg. per Kg. daily to human beings, and since in none of our studies had we given Dicumarol to dogs for as long a period as to patients (up to 90 days), an additional 6 dogs were treated daily or almost daily for an extended period, receiving after the initial dose of 5 mg. per Kg., doses of 1.5 mg. per Kg. When the prothrombin and coagulation times reached levels which made hemorrhage a possibility, the daily dose, as in human beings, was temporarily omitted for a day or longer. In these last 6 dogs the prothrombin and coagulation times were determined semiweekly. In the earlier studies these tests were made triweekly or daily. Three of these 6 dogs were killed by the intravenous administration of 1.5 gm. of nembutal at the end of a month of treatment. One of the remaining 3 dogs died with gross hemorrhage about

the neck after being bitten by another dog. The other 2 were killed after 2 months of observation. Complete post-mortem examinations, including the brain in 2 of the 6 dogs, were done, and detailed microscopic studies of the tissues were made. In this group of 6 dogs no vascular dilatation or other lesion of any of the organs was noted.

Microscopic Findings

The detailed microscopic study of the animals in this experiment included in most instances sections from heart, lungs, liver, spleen, kidney, urinary bladder, stomach, small intestine, colon, pancreas, adrenal, aorta, lymph nodes, bone marrow, areas of gross hemorrhage, and occasionally the brain. The results of this histologic study may be summarized for the first 29 animals, which received large toxic doses of Dicumarol; and separately for the last 6 dogs, which received doses within the therapeutic range.

Hemorrhages. Microscopic hemorrhages were present in almost all of the animals of the first group whether or not they had been revealed in the gross examination. These were irregularly distributed and occurred in almost all the tissues. In most instances, they were capillary or venular and numerous though not extensive.

Vascular Changes. In all of the animals of the first group rather characteristic vascular changes occurred which we designate as "toxic vascular changes." These changes were widespread in all of the animals and occurred in both systemic and pulmonic circulations; small arteries, arterioles, capillaries, venules and small veins were most seriously affected. Toxic vascular changes consist of dilatation of the vessels; marked swelling to vacuolization of the endothelium with areas of endothelial proliferation; parenchymatous, vacuolar, or fatty degeneration of smooth muscle; hyaline swelling or rupture of elastic fibers; or areas of hyaline necrosis of portions of the entire thickness of the vascular wall. In many areas small vessels were actually ruptured, and increased permeability was repeatedly demonstrated by perivascular serous transudate and diapedesis of white and red blood cells.

Renal Glomerular Lesions. Associated with these vascular changes in all of the animals were definite acute glomerular lesions: swelling of glomerular endothelium, swelling and hyalinization of the glomerular epithelial basement membrane, some swelling of the epithelium, a consequent reduction of the blood content of the glomeruli, albuminuria, and occasional small glomerular hemorrhages. Rarely one to several polymorphonuclear leukocytes were found. These acute glomerular lesions gave no indication of proliferative reaction, which might have been expected had the animals survived for a longer time.

Lymphoid Tissue Changes. Most of these animals exhibited toxic and reactive lesions in the splenic corpuscles and lymph nodes examined. These consisted of some necrosis of lymphocytes, phagocytosis of lymphocytes, hyperplasia of germinal centers, and in some instances exhaustion and skeletonization of lymphoid tissue. Toxic vascular changes were prominent in these tissues.

Liver. No consistent lesions of the liver attributable to the administration of Dicumarol were discovered, and no necrosis of the liver was found in any of the 29 dogs. Some livers showed parenchymatous degeneration, some showed fatty degeneration, and a few hydropic degeneration. None of these degenerations was present in all of the animals, and there was no zonal distribution. In several instances sufficient time had elapsed post mortem or sufficient anemia resulting from hemorrhage had occurred to be an important consideration. Because of the nonspecificity of these degenerative lesions of the liver, their irregularity of appearance and of distribution, and the frequency with which all of them appear in dogs' livers under usual laboratory circumstances, it was felt that they could not be ascribed to Dicumarol, even with the large doses used. Of even greater significance was the lack of hepatic necrosis in the series.

Other Tissues. No other lesions appeared consistently. Occasionally a dog showed a purulent bronchiolitis or other secondary infection. Numerous minor lesions were seen, usually secondary to toxic vascular changes, but these were irregular or entirely incidental in occurrence. Fat stains, glycogen stains and Mallory's connective tissue stain were used frequently to confirm the findings.

Microscopic Findings in the Second Series

Upon the 6 dogs which received Dicumarol in dosages within therapeutic range over periods of from 1 to 2 months, autopsies were performed and sections of tissues comparable to those in the first were studied. The same special stains were used.

Particular attention was given to the lesions described as characteristic in the first series. Except in 1 dog, however, no gross or microscopic hemorrhages occurred. This animal (3A) suffered extensive hemorrhage about the neck after being injured in that region by another dog. In none of the tissues from these 6 dogs, including dog 3A, were there any toxic vascular changes. The renal glomerular changes were lacking in this group. On the other hand, 5 of these dogs showed varying degrees of toxic involvement of the lymphoid tissue of the spleen and lymph nodes.

In all 6 dogs, the only hepatic lesion found was a vacuolar appear-

ance. This vacuolization of liver cell cytoplasm was probably due to glycogen, and is believed to reflect a better state of nutrition in these animals kept on a good laboratory regime than in the dogs usually used in shorter experimental procedures. It is believed that this vacuolar change is not due to Dicumarol for the additional reason that it is accompanied by no evidence of toxic vascular change.

DISCUSSION

The consistency of our observations of the pathology associated with large lethal and sublethal doses of Dicumarol in the first series of dogs would seem to indicate that they are significant. Most important of these are the definite evidences of serious damage to the small blood vessels. This damage, which is extensive in distribution, is apparently the result of specific toxicity of Dicumarol. Such pathologic changes in the vessel walls, combined with the induced reduction in prothrombin, make hemorrhages almost inevitable. That such hemorrhages, either gross or microscopic, do occur in Dicumarol poisoning is confirmed by our findings in this series of dogs.

That Dicumarol is toxic when given in large doses is further indicated by the consistent presence of toxic-reactive lymphoid tissue in the spleen, lymph nodes, lymph follicles and bone marrow. The hyperplastic reactive state of the lymphoid tissue indicates that in most instances this circulating toxin is not present in sufficient concentration to cause necrosis. And it also seems to indicate the probable site of detoxification in animals which survive.

The renal vascular changes are particularly noteworthy. These are most prominent and quite consistent in the glomeruli. The functional effects of this glomerular swelling were not studied in this series. But the morphologic changes suggest that the glomerular swelling may be of importance in various stages of acute poisoning, and there is a distinct possibility that significant secondary changes might have occurred had the animals lived longer.

We have failed to confirm other investigators' reports of liver necrosis or even to find consistent degenerative changes in the liver in Dicumarol poisoning in these dogs. We do not, therefore, agree that the lesions of primary importance are in the liver. On these morphologic grounds we question the theory that Dicumarol reduces prothrombin through destruction or injury of hepatic tissue.

The series of 6 dogs given Dicumarol in doses approximating those given human beings for therapeutic purposes contrast strongly with the larger series which were poisoned. Comparable effects on the prothrombin activity, as reflected by the prothrombin times, were seen

only in the dog that suffered trauma to the neck and died of extensive hemorrhages in that region. Yet in none of these animals were any of the lesions present which were seen in the previous series. Complete autopsies and extensive microscopic search failed to show toxic vascular change, hemorrhages, or renal glomerular swelling. However, some toxic tissue effect was noted in the hyperplastic reactive lymphoid tissue, but these changes were much less pronounced than in the previous series.

HUMAN CASES

During, and since, the period when these animal experiments were being performed, autopsies have been conducted upon five human beings, with a variety of diseases, to whom Dicumarol had been administered. To these patients the drug was given in total doses of 250 to 5820 mg. over periods of several days to several weeks. Four of them received Dicumarol up to, or shortly before, death for varying periods of time; one had received a single dose of 305 mg. 2 days before death. The gross and microscopic findings have been reviewed with special reference to morphologic evidences of Dicumarol poisoning. None of the typical lesions has been found, nor have any other lesions which could be unequivocally charged to Dicumarol. No hepatic necrosis or degeneration ascribable to Dicumarol was determined, and no secondary or chronic lesions due to Dicumarol. Hyperplastic lymphoid reaction was seen in several instances, but other changes obscured the background.

SUMMARY

In a series of 29 dogs which had received doses of Dicumarol far larger than necessary or desirable for therapeutic purposes, the outstanding morphologic evidences of poisoning were:

1. Hemorrhages, gross or microscopic
2. Toxic lesions of small vessels
3. Acute renal glomerular swelling
4. Toxic lymphoid tissue reaction

No necrosis of the liver and no consistent hepatic degenerative lesions were found.

In a series of 6 dogs which had received Dicumarol at levels of therapeutic dosage, the first three lesions listed were not seen, and the lymphoid tissue reaction was milder.

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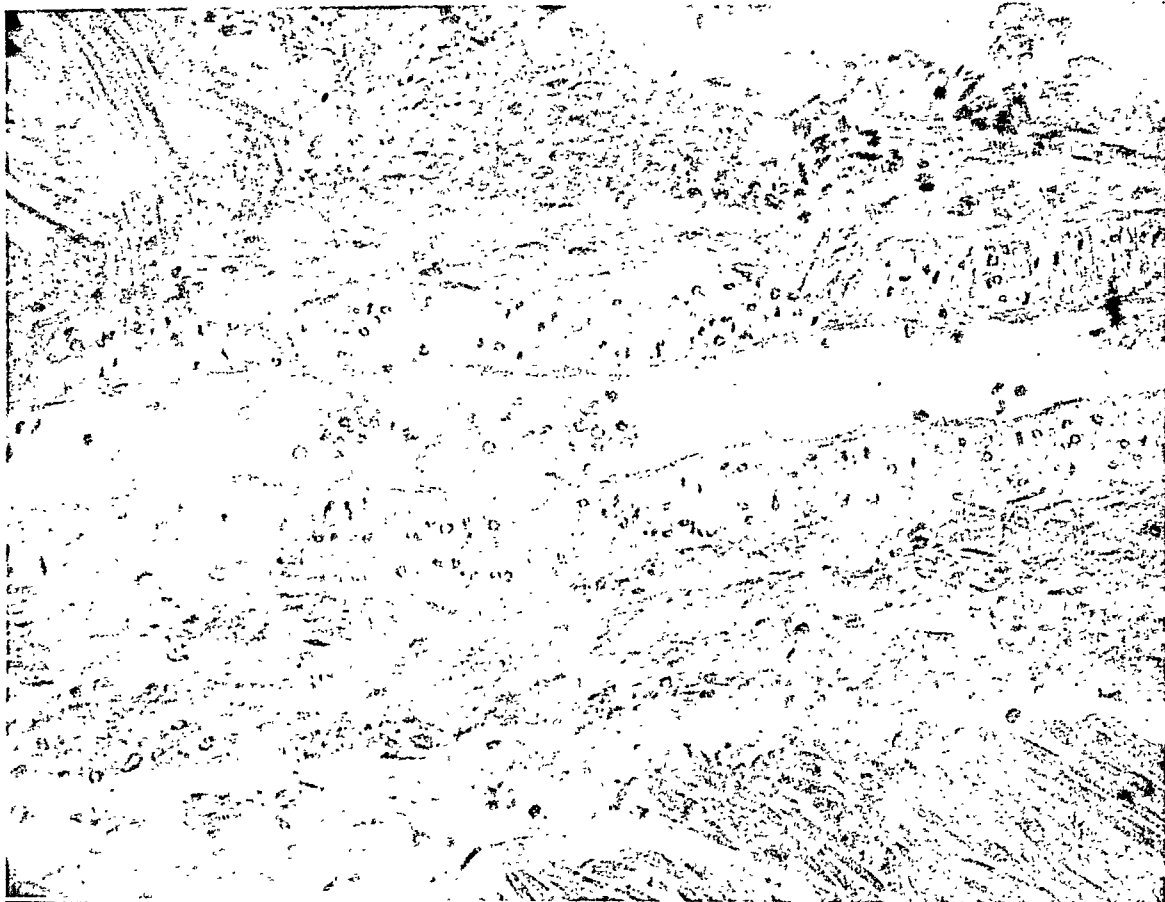
[Illustrations follow]

DESCRIPTION OF PLATE

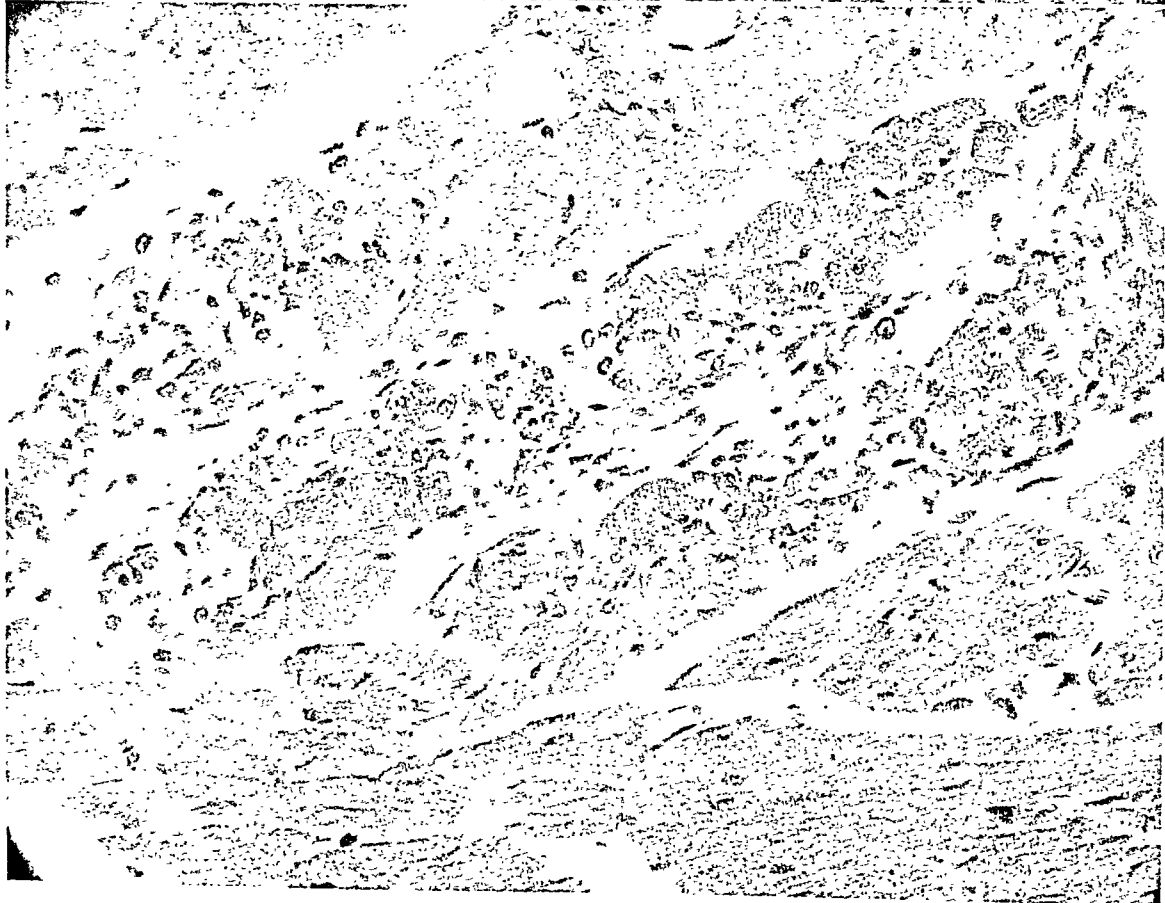
PLATE 130

- FIG. 1. Small artery in the wall of the urinary bladder of a dog poisoned with Dicumarol, showing endothelial swelling, vacuolation of smooth muscle, infiltration of vessel wall by inflammatory cells, and surrounding tissue edema. $\times 400$.
- FIG. 2. Myocardium of a dog poisoned with Dicumarol, showing endothelial swelling, capillary rupture, toxic necrosis of adjacent muscle fibers, and early inflammatory reaction. $\times 400$.

1



2



McCarter, Bingham and Meyer

Pathologic Findings After Dicumarol

EXTRACTS FROM
MINUTES OF THE MEETING OF THE COUNCIL

THE AMERICAN ASSOCIATION OF
PATHOLOGISTS AND BACTERIOLOGISTS

CLEVELAND

APRIL EIGHTH, 1944

THE AMERICAN ASSOCIATION OF PATHOLOGISTS AND BACTERIOLOGISTS

Extracts from Minutes of the Meeting of the Council
Held at Cleveland, Ohio, April 8, 1944

Present. President CANNON, Doctors FORBUS, HAYTHORN, KARSNER, MORITZ, SOULE and WELLER.

The Secretary reported that leave of absence because of military service has been granted to the following: Drs. Leo Alexander, D. Murray Angevine, William Antopol, Francis Bayless, Eustace L. Benjamin, Louis F. Bishop, Jr., Herman Bolker, Mark M. Bracken, Chester R. Brown, John W. Budd, Warren C. Corwin, Milton J. Eisen, W. Norman Elton, George H. Fetterman, Edgar C. Fielden, Harold Fink, James S. Forrester, Edward A. Gall, R. H. Goodale, Thomas R. Hamilton, Francis F. Harrison, J. Beach Hazard, Henry Horn, Cornelius A. Hospers, George J. Kastlin, Harold B. Kenton, Jack D. Kirshbaum, Leone McGregor, Abou D. Pollack, Clara Raven, Sol R. Rosenthal, Joseph E. Smadel, William S. Stanbury, M. J. Stewart, Phillips Thygeson, H. Windsor Wade, Robert J. Williams, Harold Wood.

The following were elected to membership in the Association:

LAWRENCE BERMAN	G. BURROUGHS MIDER
WILBERT OTHO BROWN	HARRY E. MORTON
ALFONS PHILIP FALKENSTEIN	BALBIR BALL GREENE NEHAUL
ROBERT A. FOX	HARRY GEORGE OLKEN
NATHAN B. FRIEDMAN	OTAKAR J. POLLAK
JOHN E. GREGORY	JOSEPH-LUC RIOPELLE
JOSEPH MACGLASHAN HILL	WILLIAM OGBURN RUSSELL
HARALD N. JOHNSON	BERT E. STOFER
EMILY NICHOLS LOEB	ROBERT E. STOWELL
ELIZABETH LOWENHAUPT	GEORGE SIEGISMUND STRASSMANN
GEORGE MARGOLIS	WALTER ALBERT STRYKER
EDMUND MAYER	FRANK THORP, JR.

JOHN LINCOLN WORK

It was voted to require payment of first year's dues of new members in order to establish membership, with understanding that the *American Journal of Pathology* will be sent for the entire year 1944, and with the

further understanding that those in military service may apply for leave of absence to begin January 1, 1945.

At their request, Drs. Percival Bailey and W. Bloom were reinstated to membership.

The deaths of the following members were recorded with deep regret:

FRANK C. ANDRUS
CARL W. APFELBACH
LEO BUERGER
GEORGE W. CRILE
JAMES EWING
KARL LOWENTHAL

FREDERIC C. NARR
G. Y. RUSK
A. V. ST. GEORGE
W. R. STEINER
LESLIE T. WEBSTER
H. G. WELLS

Dr. Malcolm H. Soule was reelected Associate Editor of the *American Journal of Pathology* for a term of one year.

Dr. Paul R. Cannon, whose term expires as a member of the Editorial Board of the *American Journal of Pathology*, was reelected for a term of six years.

It was voted that unless unforeseen circumstances arise, the annual scientific sessions of the Association will be held at the University of Chicago, Friday and Saturday, May 4 and 5, 1945. The symposium selected for the meeting is "Infectious Granulomas, Exclusive of Tuberculosis and Syphilis." Dr. Wiley D. Forbus, Professor of Pathology of Duke University, will be the referee.

The Council voted unanimously to select Dr. Ludvig Hektoen for the award of the Gold Headed Cane.

Dr. N. Chandler Foot was appointed as Chairman of the Advisory Committee of the Lymphatic Tumor Registry.

It was voted to appoint Dr. Harry Goldblatt as a new member of the Advisory Committee of the Lymphatic Tumor Registry.

It was voted that the Council of the American Association of Pathologists and Bacteriologists recommend to the Council of the International Association of Medical Museums consideration of a discussion of pedagogical and educational problems in the field of Pathology.

HOWARD T. KARSNER, *Secretary*

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THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME XX

JULY, 1944

NUMBER 4

CALCIFICATION OF THE MEDIA OF THE HUMAN AORTA AND ITS RELATION TO INTIMAL ARTERIOSCLEROSIS, AGEING AND DISEASE *

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In recent years the emphasis in the etiology of atheromatosis and arteriosclerosis has been placed on the intimal changes. This has been based mainly on the fact that numerous experiments in animals, particularly in the rabbit, have demonstrated the production of atheromatous lesions following the administration of large amounts of lipid substances such as cholesterol. However, there is also evidence that other factors play an important rôle in the genesis of arteriosclerosis and that the lipoids may be secondarily deposited in the intima. It has not been possible to show, except in rare instances, that there exists in human beings an elevated lipid content of the serum which might account for the presence of atheromatous lesions in the intima of the aorta. The experiments of Anitschkow¹ and also of Harrison² have demonstrated that the presence of medial defects in the rabbit's aorta will influence the deposition of intimal lipoids following cholesterol feeding. There are also certain histological differences between the character of the intimal lesions in experimental animals and in man, although these differences may be considered of relatively minor importance.

The association between the elastic properties of arteries and the development of the intimal lesions of arteriosclerosis has been a point of interest for many years. It appears to have been first stressed by Polotebnow,³ in 1868, who observed that a sclerotic artery could be stretched only one-fourth as much as a normal one. Kaufmann⁴ found that the size of the aorta depended on age and body build, the enlargement of the aorta with age being due to a loss of elasticity. More recently the experiments of Wilens⁵ showed that with advancing age there is a progressive loss of elasticity which varies in degree in differ-

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ent areas but proceeds at a constant rate for a given area and affects all persons to approximately the same degree. He has further observed that the development of intimal plaques is not directly related to this loss of elasticity, for a greatly thickened intima can restrict the elasticity of the media only to a relatively slight degree. Loss of elasticity of the media proceeds as rapidly in those subjects who develop slight intimal atheromas as in those who exhibit profound changes. The earliest and largest intimal accumulations of lipoids appear in those areas which are subject to the earliest and most marked loss of elasticity.

The theory that loss of elasticity and weakening of the vessel wall are the primary factors that precipitate all subsequent intimal lesions is an old one. It was propounded by Thoma and Kaefer,⁶ in 1889, and has been supported by Faber,⁷ Klotz⁸ and, more recently, by Wells.⁹ The latter stated that the changes in the physicochemical properties of arteries support the view that arteriosclerosis depends primarily on the reduction in elasticity of the media, and that the subsequent changes seem to be due to the yielding of the media. To support this theory numerous lesions have been described as occurring in the media; among these can be listed swelling, fragmentation, diminution in volume, fatty infiltration, and calcification of elastic fibers. The problem is apparently complicated by the belief that there is considerable diversity in the vascular manifestations, depending upon the site and type of vessels involved. Thus, Winternitz, Thomas and LeCompte¹⁰ have recently restated a generally accepted concept that "the muscular arteries, for example, are very prone to undergo medial change ending in calcification, without necessarily involving either the intimal or adventitial coats, whereas this type of change in the larger elastic arteries is rare."

However, calcification of the media of the aorta has been observed by Klotz,⁸ Ribbert,¹¹ Ravault,¹² Farkas and Fasal,¹³ as well as by Faber.⁷ Of these investigators, only Faber believed that there was a relationship between calcification of the media of the aorta and the production of intimal arteriosclerosis; the others could find no direct parallelism between the amount of calcium deposited in the media and arteriosclerosis of the intima. In all these investigations it was recognized that calcification of the media rarely occurred in young persons, but no organized attempt was made to correlate this change with age. It would thus appear that while calcification of the media of the human aorta has been recognized, little is known of its significance. Faber, as well as Farkas and Fasal, attempted to study calcification of the media of the aorta and its relation to ageing and disease, but they were unable to reach any definite conclusion from the limited number of cases studied.

In the course of study of human aortas from routine autopsies, we noted the frequent occurrence of a blue-staining, finely granular material in the media of the aorta which was apparently similar in character to that described by Björling¹⁴ as mucoid degeneration. However, subsequent analysis by micro-incineration showed this material to be composed largely of calcium, and on the basis of this observation it was decided to investigate the relationship of calcification of the media of the aorta to intimal arteriosclerosis, ageing and disease.

MATERIALS AND METHODS

A preliminary experiment was carried out in an attempt to determine whether the dark blue granular material in the media of aortas stained with alkaline Delafield's hematoxylin was calcium. Sections were made from 10 aortas imbedded in paraffin in the usual manner. These were mounted on slides for study by micro-incineration, and control slides were stained with alkaline Delafield's hematoxylin and eosin. The technic of micro-incineration was the same as that developed by Scott,¹⁵ and also employed by one of us (Lansing).¹⁶ Examination of these incinerated preparations by darkfield microscopy revealed areas containing large amounts of white ash which corresponded in general to the areas of dark blue granular material in the hematoxylin and eosin preparations. This white ash has been identified clearly as calcium by Lansing and Scott.¹⁷ That the blue granular material represents calcium is also indicated by the observation that this staining reaction can be prevented by decalcification in dilute nitric acid (Figs. 7 and 8).

In a second experiment 50 specimens of aortas of various ages taken from the proximal part of the arch, and showing varying degrees of blue-granular material in the media, were examined also by the technic of micro-incineration. It was noted that the areas showing the greatest concentration of calcium in the micro-incinerated preparations corresponded to the sites of deposition of the blue-granular substances in the hematoxylin and eosin preparation. There were, however, other areas in the micro-incinerated preparation in which there was more finely dispersed calcium, and these could not be identified in the hematoxylin and eosin preparations. This indicates the greater sensitivity of the method of micro-incineration for the demonstration of calcium.

With the previous two experiments as a basis, a statistical analysis was carried out for the purpose of determining the relationship of age and disease to calcification of the media. For this purpose we used specimens from 582 aortas, removed from the proximal portion of the arch and stained with alkaline Delafield's hematoxylin and eosin. This

number included the 60 specimens used in the two preliminary experiments. It should be stated that in those cases in which the hematoxylin and eosin stain failed to reveal evidence of calcification of the media, either micro-incinerated preparations were made or the slides were restained. This was done because it was noted that when the hematoxylin became old, or had lost some of its alkalinity, it failed to reveal the presence of the blue-granular material in the media. Also, in some cases in which autopsy had been performed 18 or more hours after death, even fresh hematoxylin preparations failed to show evidence of calcium. In all of these cases, however, the presence of calcium in the media could be demonstrated in micro-incinerated preparations.

The sections were arbitrarily graded as negative, 1 plus, 2 plus, or 3 plus (0, +, ++, or +++) in accordance with the degree of calcification of the media; photomicrographs illustrating these grades, both by micro-incineration and by hematoxylin and eosin staining, are shown in Figures 1 to 9.

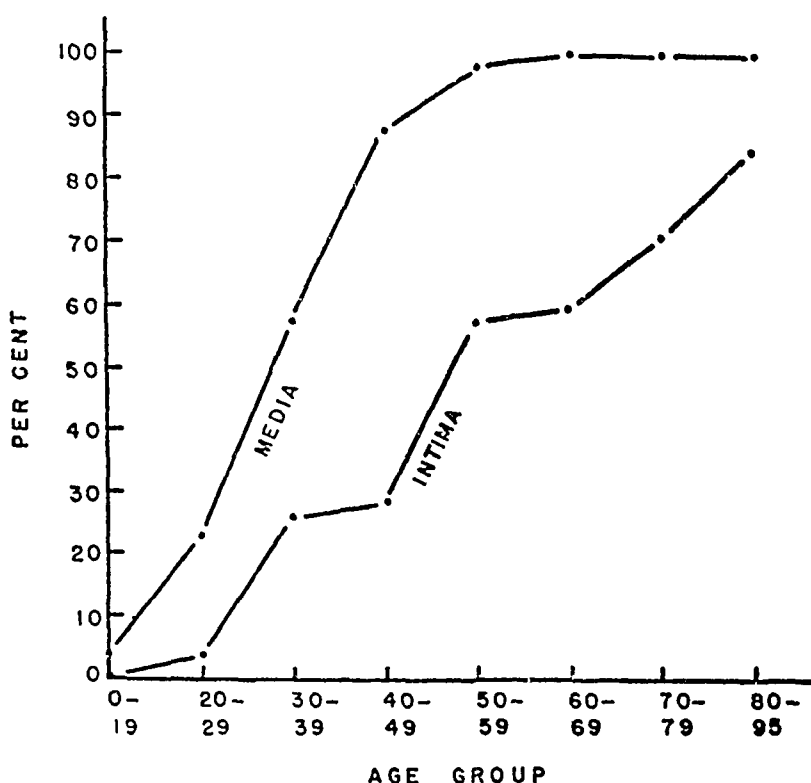
In a final experiment various levels through the whole length of 6 aortas were studied in order to determine whether or not the intensity of calcification of the media is uniform throughout the length of the aorta, as well as to determine if there is any correlation between the intensity of calcification of the media and the site of formation of intimal plaques.

RESULTS

In 60 aortas we carefully compared the site of deposition of the blue-granular material in hematoxylin and eosin sections with the areas of calcification in corresponding micro-incinerated preparations. In those showing a slight degree of calcification of the media, it could be seen that the calcium was deposited between the muscle fibers; this distribution would correspond to the areas usually occupied by elastic fibers. With progressive increase in the amount of calcium, the areas involved became more extensive, and in pronounced cases the cellular structure of the media became entirely obliterated. In the latter instances it was possible to conclude that both muscle and elastic fibers were heavily infiltrated with calcium. This can be seen in Figures 7 and 9. Occasionally in senile specimens discrete concretions of calcium were observed in addition to the general 3 plus calcification of the media. However, such condensations occurred relatively infrequently.

Specimens taken through various areas of 6 whole aortas, from subjects ranging in age between 35 and 83 years, were studied by micro-

incineration. The areas studied included the proximal part of the arch free of intimal plaques, the abdominal aorta free of intimal plaques, and the abdominal aorta including intimal plaques. In general, the intensity of calcification of the media was greater in the abdominal than in the thoracic portion of aortas taken from subjects 35, 55 and 63 years old. In the remaining 3 subjects, 70, 76 and 83 years old, the concentration of calcium in the media was so great throughout the aorta that it was not possible to estimate quantitative differences between the thoracic and abdominal portions. In the three younger cases it could be determined also that the concentration of calcium in the abdominal portion of the aorta was greater in the area immediately under an intimal plaque than where there was no evidence of intimal



Text-Fig. 1. The age-incidence of medial calcification and of intimal sclerosis, based on 540 aortas.

proliferation, while in the three older specimens the concentration of calcium throughout the media was so great that such a difference was no longer discernible.

The age-incidence of calcification of the media obtained from the examination of 540 aortas of various ages is shown graphically in Text-Figure 1. Prior to 20 years of age medial calcification occurred in only 4 per cent of the cases; between 20 and 30 years this increased

to 58 per cent; between 40 and 50 years 98 per cent showed this change, and after 50 years of age calcification of the media was present in all cases exclusive of certain instances in which there were other diseases of the media. It should be noted that these figures do not take into account the intensity of calcification of the media; they present only the incidence. The data in Table I show that the intensity of calcification of the media as well as the frequency of its occurrence increases with age. Thus, calculations from the data in this table show that prior to 50 years of age 56 per cent of the cases showed no medial calcification, 32 per cent showed slight (+) calcification, and only 12 per cent showed marked calcification (++ and +++). After 50

TABLE I

Age Distribution and Correlation of Calcification of the Media and Intimal Proliferation in the Human Aorta*

Age groups	No intimal lesions				With intimal plaques				Calcified plaques			
	0*	1	2	3	0*	1	2	3	0*	1	2	3
0-19	47	2										
20-29	20	4	1			1						
30-39	16	12				2	4			3		1
40-49	5	20	7			2	3	1		5		
50-59		23	11	3	1†	14	11	3	1	10	6	5
60-69		32	15	7		14	13	6		21	20	7
70-79		20	9	3		8	10	4		22	22	14
80-95		4	2	1		1	3	1		13	11	11

* Medial changes are graded 0, 1, 2, and 3 in accordance with the degree of calcium deposition.

† Connective tissue penetration of the media.

years of age there were no cases free of this change, while 48 per cent had slight calcification (+) and 52 per cent showed a marked deposition of calcium in the media (++ and +++). The influence of age on the intensity of medial calcification is shown also in the first two columns of Table II, where it can be seen that there is in both sexes a progressive increase in the mean intensity of calcification with increasing age, at least up to 59 years. Apparently the increase with age is less definite after 60 years.

In Table II we have analyzed statistically the intensity of medial calcification of the aorta on the basis of sex and of various diseases of which there were sufficient cases to allow for the determination of significant differences. There is no significant difference between the intensity of calcification of the media in corresponding decades in the two sexes. The cases in which death was due to a rapidly fatal accident or to an acute infectious disease were used as controls since these would not be expected to have an influence on calcification of the

TABLE II
The Influence of Sex and Disease on the Graded Incidence of Deposition of Calcium in the Media of the Aorta as Correlated with Age

Classification	Age groups							
	0-19	20-29	30-39	40-49	50-59	60-69	70-79	Over 80
Females (all cases)	0.0 ± 0.0	0.4 ± 0.2	0.8 ± 0.2	1.2 ± 0.1	1.7 ± 0.3	1.6 ± 0.1	1.7 ± 0.1	1.8 ± 0.2
Males (all cases)	0.1 ± 0.1	0.1 ± 0.1	0.6 ± 0.2	1.2 ± 0.1	1.5 ± 0.1	1.7 ± 0.1	1.8 ± 0.1	2.1 ± 0.2
Accident or acute disease	0.0 ± 0.0	1.0 ± 0.2	1.2 ± 0.1	1.6 ± 0.1	2.0 ± 0.2	1.9 ± 0.3
Tuberculosis	0.1 ± 0.1	0.3 ± 0.2	0.6 ± 0.1	1.2 ± 0.3	1.4 ± 0.2	1.6 ± 0.2	1.9 ± 0.2
Cancer	1.0 ± 0.6	1.1 ± 0.2	1.8 ± 0.1	1.8 ± 0.1	1.3 ± 0.1	2.3 ± 0.3
Nephrosclerosis and/or hypertension	2.8 (4)	1.6 ± 0.2	1.8 ± 0.3	1.5 ± 0.1	1.5 ± 0.2	1.8 ± 0.3
Coronary thrombosis, cerebral thrombosis and hemorrhage	1.3 (4)	1.6 ± 0.2	1.7 ± 0.2	1.9 ± 0.2	2.1 ± 0.4
Syphilitic aortitis	0.0 (3)	0.0 ± 0.0	0.2 ± 0.1	0.4 ± 0.2	0.1 ± 0.1

Figures in parentheses represent the number of cases when they were relatively few.

media. When this group is compared with the two groups according to sex, it may be noted that the mean values for the three groups are essentially the same for corresponding age groups except for the decade between 50 and 60 years. Here the mean value for the group with accidental death is somewhat lower than those generally obtained in males and females of corresponding age; this difference, however, is of doubtful statistical significance and may be due to the effects of other diseases included in the two groups according to sex, as will be noted later. A comparison of the data from patients dying of tuberculosis with those obtained from groups with deaths from accident and acute diseases does not reveal any significant differences. There were no patients below 30 years of age dying of cancer. The mean values of the various age groups of cancer patients, when compared with the group with accidental death, were essentially similar except during the decades of 50 to 60 and 70 to 80 years; in the former decade the mean intensity of calcification in cancer patients was greater, while in the latter it was lower, than in the group with accidental death. Another group was composed of patients dying of coronary arterial thrombosis and cerebral arterial hemorrhage or thrombosis. As would be expected, there were none younger than 40 years of age in this category, and only 4 in the decade from 40 to 50 years. There were no significant differences between this group, the group with accidental death, or the groups according to sex.

The most striking results were obtained from a comparison of the intensity of medial calcification in subjects with syphilitic aortitis and all other groups. Of 42 specimens of syphilitic aortitis studied, 33 showed no calcification of the media and only 9 showed it to a very slight degree (+). Characteristic of these cases was partial replacement of the media by fibrous tissue; an example of this is shown in Figure 10. It may be noted here that there were two other cases with connective tissue penetration into the media which did not show the inflammatory change characteristic of syphilitic aortitis and in which no definite etiology could be established; here also no evidence of calcification of the media could be obtained. In Figure 11 an incinerated preparation of typical syphilitic aortitis is shown; despite the advanced age of this subject (72 years), the calcium content of the media is essentially comparable to that of a child (*cf.* Fig. 2).

DISCUSSION

The term "arteriosclerosis" has generally been used to describe various changes in the arteries which lead to their loss of elasticity. In the aorta it denotes a thickening of the intima produced by a new forma-

tion of connective tissue in which there may be found small and large wandering cells laden with fat. In later stages the thickened intima becomes hyaline or necrotic about the more abundant accumulations of fat, and secondary areas of calcification may occur. Medial changes are usually held to be the result of encroachment of the intimal plaques upon the media. Although several investigators have described the frequent occurrence of calcium deposits in the media of the human aorta, this phenomenon has not received general recognition, probably due to a tendency to look for gross or relatively homogeneous concretions such as the calcium plaques which occur in the intima of the aorta and in the media of muscular arteries (Mönckeberg's sclerosis). Calcification of the media of elastic arteries has been described (see Introduction) as being essentially microscopical and has been observed only by the use of special stains or micro-incineration. However, we have observed in a few cases extreme calcification of the media leading to the formation of concretions. From a physiological point of view, the degree of calcification observed in these experiments can be expected to produce functional changes in the contractility of the aortic wall.

Our studies tend to confirm the observations of Ravault¹² that calcification of the media of the aorta is primarily associated with the elastic elements, since in the early stages calcium is deposited between muscle fibers rather than inside the muscle cell. It is of interest in this respect that in syphilitic aortitis, in which the elastic elements of the media are destroyed, the amount of calcium is markedly less, or it may be absent. In more severe changes, the calcium becomes generally deposited and involves all of the elements composing the media. However, Hass¹⁸ has observed the formation of collagenous splints in the media, and the deposition of calcium in these structures as well as in the elastic lamellae must be considered as a possibility.

It is interesting to note that Shelling, Asher and Jackson,¹⁹ as well as Johnson,²⁰ have observed calcified and degenerative arterial lesions in human beings with adenomas of the parathyroid glands, and similar changes have been described in dogs following the administration of large amounts of parathyroid hormone (Hueper,²¹ Learner,²² McJunkin, Tweedy and Breuhaus²³). While the experimental lesions mainly involve the media, in man the intima is affected as well as the media. A more extensive lesion involving both the intima and media of elastic as well as muscular arteries has been produced in rabbits, cats, dogs and rats by the administration of large amounts of vitamin D (Kreitmair and Hintzelmann,²⁴ Schmidtman,²⁵ Hueper,²⁶ Ham and Lewis,²⁷ Ham and Portuondo,²⁸ Shohl, Goldblatt and Brown,²⁹ and

others). Hueper²⁶ has observed similar results following a lengthy exposure of rats to ultraviolet irradiation. It should be noted that in these lesions there are areas of intimal proliferation in close proximity to the areas of calcification of the media.

We have seen in the present observations a step by step increase in the amount of calcium deposited in the media of the aorta with increasing age. Wilens⁵ has demonstrated that in the human aorta the elasticity progressively decreases with age and is primarily dependent upon changes in the elastic elements in the media. Similarly, Saxton³⁰ has studied the extensibility of the rabbit aorta with respect to age and has been able to show that this vessel becomes more extensible with increasing age; it also becomes less able to return to its original circumference after stretching. However, the results of this investigator suggested that the rabbit aorta does not age as rapidly as the human aorta and is still a relatively young structure at the end of the life span of this species. Hass¹⁸ has used purified elastic tissue preparations, and has observed that the extensibility of purified networks of elastic tissue is greatest in young specimens and usually decreases with age, although occasional aged elastic systems have the characteristic high extensibility of youthful tissue. Unfortunately, it cannot be ascertained from Hass' experiments what rôle calcium plays in this change in extensibility because the method used in the purification of elastic tissue removes the calcium from this tissue. However, it is very likely that with the infiltration into the media of large amounts of calcium with age there would be a profound diminution in both elasticity and contractility of the aorta. Significantly, the curve of reduction of elasticity with age, as demonstrated by Wilens,⁵ closely parallels the curve of intensity of calcification of the media with age in the present experiments.

As stated previously, the theory that loss of elasticity and weakening of the vessel wall are the primary factors which precipitate the formation of subsequent intimal lesions has been considered for a long time. The chief supporters of this concept have been Thoma and Kaefer,⁶ Faber,⁷ Klotz,⁸ Wells,⁹ and, more recently, Wilens⁵ and Hass.¹⁸ The latter investigator believes that "the intimal changes represent a fortuitous accumulation of lipids in a collagenous splint that is deposited in response to a primary failure of medial systems to maintain integrity of function in the presence of imposed tensions." Most of the theories concerning the focal nature of early atheromatous plaques are based on the assumption that there are certain sites subject to particular stresses and strains. Some investigators such as Duguid³¹ and Moschowitz³² believe that this leads to a localized impairment of elasticity

followed by fibrous overgrowth of the intima at that site, or to a wrinkling with formation of connective tissue interstices. Other investigators stress primarily the intimal changes. Thus Aschoff³³ described swelling of the ground substance, while Krafka³⁴ observed separation or actual intimal herniation. Moon³⁵ placed emphasis on a local anemia, while Winternitz, Thomas and LeCompte¹⁰ described in great detail the increased intimal vascularity and hemorrhage. It is particularly the latter group of investigators who have demonstrated the rich network of small vessels which supply the arterial wall; some of these are derived from the vasa vasorum in the adventitia, while others have their origin as tiny openings in the endothelial lining of the aorta. These vessels are generally composed of a single layer of endothelial cells and depend upon the contraction of the aorta to propel their contained blood. It then becomes apparent how a change in the elasticity and contractility of the aortic wall would influence the rate of flow of blood through these small vessels. A diminution in contractility could account for a hemostasis which would result in small thrombi and hemorrhages which Winternitz, Thomas and LeCompte described as the earliest changes in the formation of atheromatous plaques; it would also account for a diminution in the amount of oxygen supplied to the intima to which Hueper²⁶ attributes importance in the formation of intimal plaques. Recently Wilens³⁶ has immobilized segments of vessels by placing silver cuffs about the femoral and carotid arteries of rabbits. This produces an adventitial thickening and fibrosis, and a thinning of the media due to atrophy of smooth muscle and condensation and fragmentation of elastic fibers. He then observed that cholesterol feeding usually leads to a selective localization of lipids in the intima of arteries at the region of the cuffs. Two observations in the present series may be in essential agreement with the interpretation that local immobility may influence the site of formation of intimal plaques. Although we have studied only 6 complete aortas, it appears that the abdominal portion undergoes a more pronounced degree of calcification of the media than does the thoracic segment; it is generally agreed that the intimal involvement in arteriosclerosis is more extensive in the abdominal than in the thoracic part of the aorta. In addition, in 3 cases we have observed that within a single aorta calcification of the media is more intense in the immediate vicinity of intimal plaques than elsewhere. The first of these two observations is contrary to a previous observation by Ravault¹² who noted a higher degree of calcification in the thoracic than in the abdominal portion of the aorta.

The assumption that in the aorta medial involvement is secondary to intimal changes is without support if the present results are valid. It

would appear more likely that intimal plaques are a result of medial injury plus, probably, other localized conditions. This contention is supported by the observations that calcification of the media precedes the formation of intimal plaques and that intimal plaques do not occur without medial calcification or some other injury to the media.

The present experiments also show that calcification of the media of the aorta is apparently not influenced by sex and by most of the diseases analyzed in our statistical data. Chronic disease *per se* apparently has no influence on this change. However, the mechanism of calcification of the media may be influenced by certain diseases. Thus, in the analysis of the 42 cases of syphilitic aortitis, 33 cases show no evidence of calcification, while in 9 cases there was only a mild degree of this change. Characteristic of syphilitic aortitis is the breakdown of the muscular and elastic elements of the media and the infiltration of scar tissue. The end-product of syphilitic aortitis, namely, the scarring of the media, results in a disruption of the normal vasa vasorum as well as a loss of contractility and elasticity. This can be expected to produce an effect upon the intima comparable to that of calcification of the media; and, indeed, thickening of the intima is a common finding in syphilitic aortitis, although the plaques may not become calcified as readily as those seen in arteriosclerosis. Also characteristic of syphilitic aortitis is the fact that plaques are more concentrated in the thoracic portion of the aorta, and therefore it would be of interest to determine if there is any difference in the degree of scarring and decalcification between the thoracic and abdominal portions of the aorta. This we hope to do in future experiments.

The data on hypertension lead to the interesting observation that calcification of the media of the aorta in the third, fourth and possibly the fifth decades is more pronounced than in the other diseases studied. It cannot be stated at present whether this is the effect of an existing hypertension or whether it is a factor in the etiology of the latter disease. However, it is conceivable that calcification of the media of the renal artery resulting in relative hemostasis could have an effect similar to that of the Goldblatt kidney. This also must await further investigation.

We have seen, therefore, how calcification of the media of the aorta may play a specific rôle in the genesis of arteriosclerosis. But the present observations also have a broader biological significance, namely, their relationship to processes of ageing in general. The present work demonstrates that the variations in frequency of calcification of the media as well as in the intensity of this phenomenon are correlated with ageing. The increase in calcium deposition in the soft tissues in human

beings is entirely in line with the fact that the calcium concentration increases with age in a variety of tissues and organs of various species. (See Lansing¹⁶ for a review of the literature on this subject.) Calcification of the media of the aorta, in particular, has been seen in a wide variety of lower mammals and birds by Fox.³⁷ Barnes³⁸ has observed that in rats the incidence of calcification of the heart is an increasing function of the age at death. It has been suggested by Lansing¹⁶ that this increase in calcium is a general characteristic of the ageing process. He has demonstrated that calcium increases with age not only in the vertebrates but also in invertebrates and even in plants. It is interesting to note that the age-intensity curve of medial calcification of the aorta (Table II) closely parallels the age-calcium concentration curve which he obtained on the water plant, *Elodea*. It appears, therefore, that we are dealing with a fundamental process in the biology of ageing, which in the specific instance of the aorta may result in secondary intimal changes producing the phenomenon of arteriosclerosis.

SUMMARY

The frequency of occurrence and the influence of age, sex and disease on calcification of the media of the human aorta were studied by means of sections prepared by hematoxylin and eosin staining and by micro-incineration. The results showed that calcification of the media precedes the formation of intimal plaques; that medial calcification occurs more frequently than do intimal plaques; that intimal plaques do not occur without calcification of the media or other medial change such as syphilitic aortitis, or marked connective tissue infiltration of the media; and that within a single aorta medial calcification is probably more intense in the immediate vicinity of an intimal plaque than elsewhere. In a few observations it was noted also that calcification of the human aorta was more pronounced in the abdominal than in the thoracic portion of the aorta.

Calcification of the media of the aorta was shown to be primarily a function of age and was not influenced by sex and various chronic infectious diseases. However, specimens from hypertensive persons between the ages of 30 and 60 years showed considerably more medial calcification than did the "controls." Of 42 cases of syphilitic aortitis, 33 showed no medial calcification and 9 showed only slight calcification of the media.

The relationship between calcification of the media of the human aorta and the loss of elasticity and contractility with age, as well as the possible relationship of these changes to the formation of intimal plaques, is discussed.

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[Illustrations follow]

DESCRIPTION OF PLATES

PLATE 131

- FIG. 1. Section of the aorta of a 14-year-old male stained with hematoxylin and eosin. There are no abnormal deposits in the media. $\times 90$, thickness $4\ \mu$.
- FIG. 2. Section of the aorta of a 14-year-old male prepared by the microincineration technic. The white ash represents deposits of calcium which correspond to the location of the nuclei in hematoxylin and eosin specimen. $\times 90$, thickness $4\ \mu$.
- FIG. 3. Section of aorta of a 40-year-old male stained with hematoxylin and eosin. A few plaque-like deposits in the media can be seen. This illustrates a 1 plus (+) deposition of calcium. $\times 90$, thickness $4\ \mu$.
- FIG. 4. Section of aorta of a 38-year-old male prepared by the microincineration technic. The deposits of calcium in the media are larger than those seen in Figure 2. This illustrates a 1 plus (+) deposition of calcium. $\times 90$, thickness $4\ \mu$.

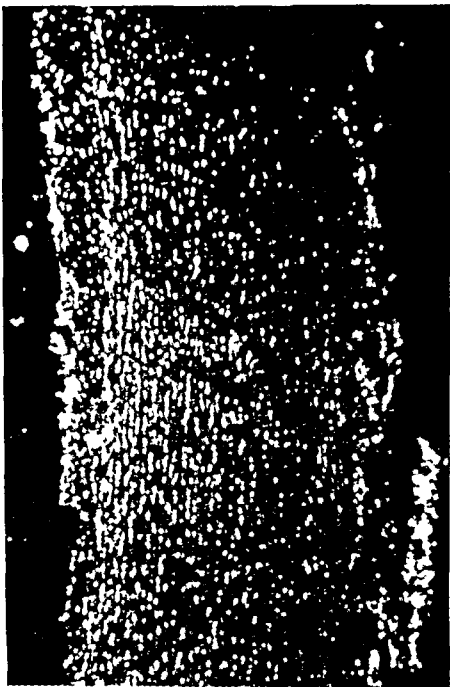
3



4



1



2

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PLATE 132

- FIG. 5. Section of aorta of a 53-year-old male stained with hematoxylin and eosin. There is an increase in the number and size of calcium deposits over those seen in Figure 3. This illustrates a 2 plus (++) deposition of calcium. $\times 100$, thickness 4 μ .
- FIG. 6. Section of aorta of a 49-year-old male prepared by the microincineration technic. The deposits of calcium are large and confluent. This illustrates a 2 plus (++) deposition of calcium. $\times 100$, thickness 4 μ .

5



6

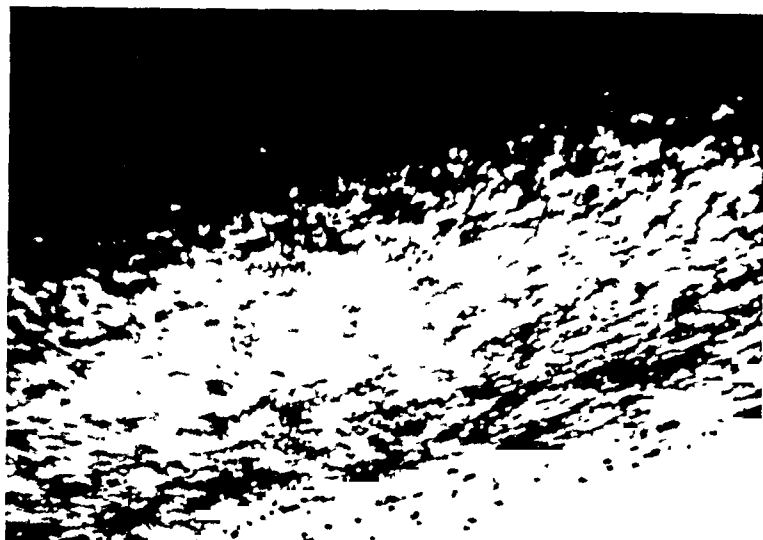
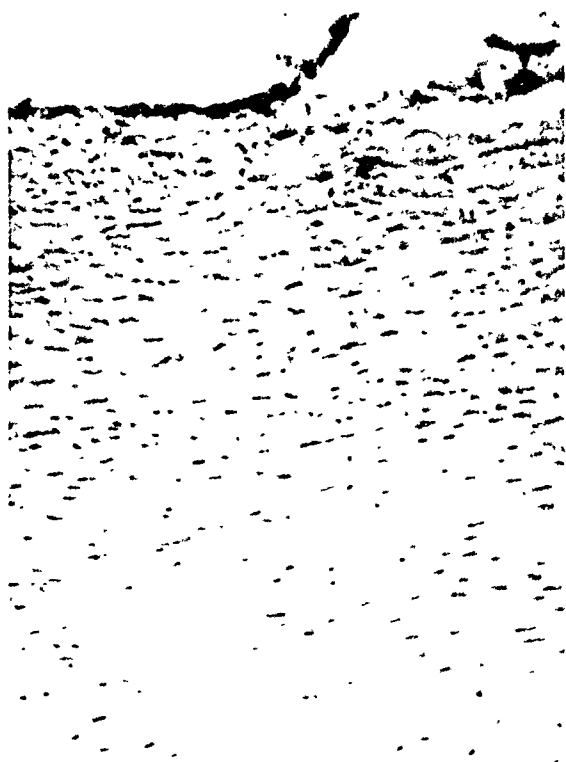


PLATE 133

- FIG. 7. Section of aorta of an 80-year-old male stained with hematoxylin and eosin. A large confluent area of calcium in the media can be seen. This illustrates a 3 plus (+++) deposition of calcium. $\times 100$, thickness $4\ \mu$.
- FIG. 8. Same specimen as that shown in Figure 7, after decalcification with dilute nitric acid. This illustrates the removal of the blue-granular material from the media by decalcification.
- FIG. 9. Section of aorta of a 75-year-old male prepared by the microincineration technic. This demonstrates a marked deposition of calcium in the media, and represents a 3 plus (+++) deposition of this substance. $\times 100$, thickness $4\ \mu$.

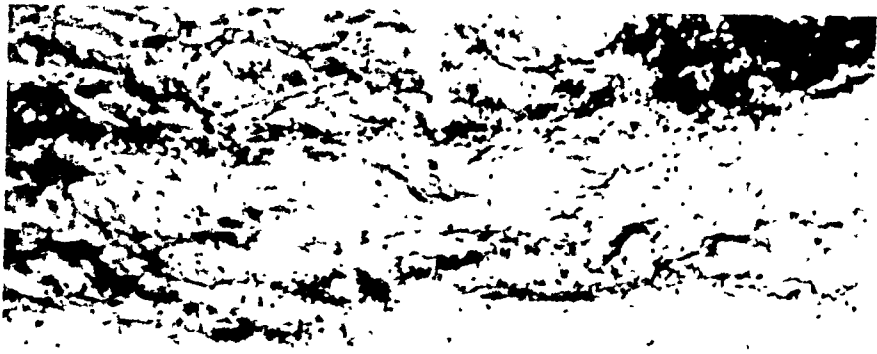


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Medial Calcification and Intimal Sclerosis

PLATE 134

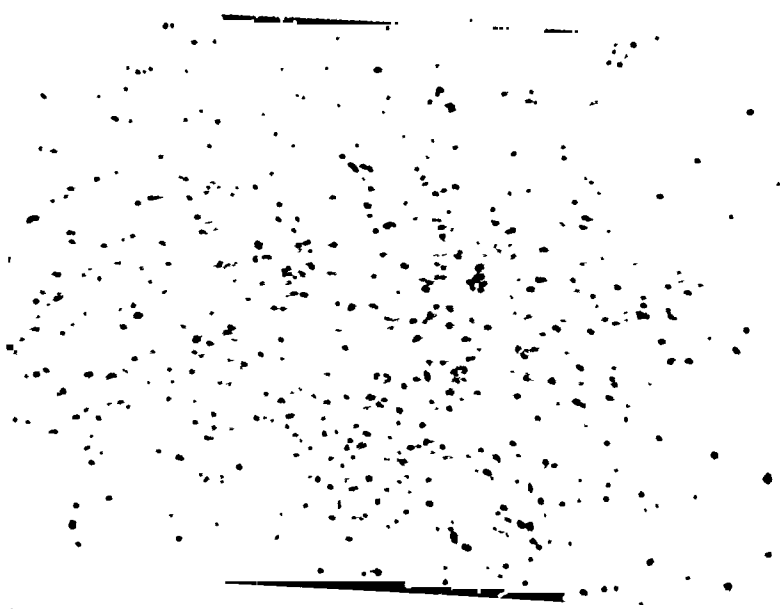
- FIG. 10. Section of aorta of a 72-year-old male stained with hematoxylin and eosin. There is a complete absence of calcareous patches in the media. A transverse medial scar is present. The adventitia, infiltrated with lymphocytes, is at the top of the figure. $\times 100$, thickness $4\ \mu$.
- FIG. 11. Same specimen as that shown in Figure 10 prepared by the microincineration technic. A marked diminution in calcium content of the media is apparent. $\times 100$, thickness $4\ \mu$.



11



11



CUSHING'S SYNDROME WITH POSSIBLE PHEOCHROMOCYTOMA

REPORT OF A CASE *

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The following case is reported because it represents a clear-cut example of "pituitary basophilism" without adenoma of the pituitary gland but with a tumor of the adrenal of uncertain histogenesis, perhaps of medullary origin.

REPORT OF CASE

Clinical History. The patient (F. S. H. no. 3289), was a housewife, 31 years old, of German ancestry who was admitted on June 20, 1942. There was a family background of mental disease; the maternal grandfather and a maternal aunt had died in psychiatric hospitals, another maternal aunt had had a "nervous breakdown," and a sister had been hospitalized since 1938 with a diagnosis of dementia praecox, catatonic type.

Nothing unusual was elicited concerning the patient's early life. She was married in 1937. For 3 years, beginning in 1936, she had had several attacks of renal colic and passed some stones. Her menstrual periods had begun at age 14 but since the age of 20 had been occurring only every 2 or 3 months and the flow had been scanty. Endocrine therapy had no apparent effect. Some months after her marriage she began to put on weight and to grow a beard. In January, 1942, her local physician found her "literally swollen like a balloon," apparently from edema. She was hospitalized and the swelling subsided somewhat, leaving striae on the abdomen. At this time urinary symptoms were indefinite. She was found to have a blood sugar ranging around 150 mg. per cent and was put on a diabetic diet with insulin. She was started on 35 units of insulin, but this seemed to be too much, and the dose was progressively cut to 15 units daily. She was given stilbestrol for her amenorrhea, which was now complete, without effect. Following discharge from the hospital she apparently had several insulin shocks. She had a persistent hypertension. For some months she was under treatment for vaginitis (*Trichomonas vaginalis*) by her family physician. He felt sure that, during the few years the patient was under his care, the clitoris had about doubled in size, reaching finally a diameter of about 1 cm. On June 14, 1942, he was called to see the patient, who was apparently in a state of insulin shock. Her systolic blood pressure was 130, and diastolic, 80, unusually low for her, and she talked in a confused manner. After admission to the Danbury Hospital she became noisy, talked about machines working on her, and showed alternately a ravenous appetite and a disinclination to eat. Frequently she would seize food from a tray and bolt it without chewing. At times she ran screaming back and forth through the halls and on one occasion tried to jump from a window. Her blood pressure was 150/90 on several occasions, and at one time rose to 174/120. The blood sugar ranged from 120 to 182 mg. per cent. She was put on a regime of 25 units of protamine zinc insulin before breakfast, and this was later increased to 35 units.

On admission to the Fairfield State Hospital on June 2, 1942, she showed a masculine distribution of hair, with hirsutism of face and body, obesity confined

* Received for publication, July 29, 1943.

to the head, neck and trunk, a peculiar moon-like, purplish, cyanotic appearance of the face, acne of face and body, and moderate exophthalmos. There were many purplish striae on the abdomen. Blood pressure was 150/100. Abdominal reflexes were absent, the gait was slow and on a wide base, and there was a suggestive Romberg sign. The ocular fundi appeared negative.

The patient seemed uninterested in her appearance and was apathetic. She wandered about aimlessly, with shuffling gait and arms hanging at her sides. Occasionally she assumed an almost catatonic posture, with her hands in her lap and eyes immobile. She answered questions fairly coherently, but occasionally spoke of a machine working on her.

Both remote and recent memory were fairly well preserved. She repeated seven digits forward but was unable to repeat any backward. Answers to simple arithmetical problems were fairly accurate but delayed. She said that ever since her menstrual periods stopped in January, 1942, she had been unable to concentrate.

The patient continued to be somewhat confused. Shortly after admission she complained of sudden pain in the right chest, and her temperature rose to 101.2° F. A roentgenogram revealed increased density, obscuring the lower portion of the right lung, and, in the upper thorax, multiple healed fractured ribs on both right and left. On June 30, 1942, an indurated area in the right axilla was drained, yielding pus which showed on smear gram-positive cocci and gram-negative rods. On July 2, 1942, the temperature rose to 105° F. She complained of dyspnea. On July 4, 1942, she died rather suddenly, a final temperature of 107.2° F. being recorded.

Laboratory Findings

Urine

	<i>Specific gravity</i>	<i>Albumin</i>	<i>Sugar</i>	<i>Acetone</i>	<i>Sediment</i>
6/25/42	Negative	Negative
6/30/42	1.012	++	+	15-20 white blood cells per field; 3-10 red blood cells per field; <i>Trichomonas vaginalis</i>
7/2/42	++++	Negative	
7/4/42	++	Negative	

Blood Cells

	<i>Red blood cells*</i>	<i>White blood cells</i>	<i>Polymorphonuclear leukocytes</i>	<i>Lymphocytes</i>	<i>Mono-nuclear leukocytes</i>	<i>Smear</i>
6/22/42	4,400,000	7,900	83% (segmented, 77%; nonsegmented, 6%)	11	6	
7/2/42	9,300	91% (segmented, 69%; nonsegmented, 22%)	4	1	3 metamyelocytes, 1 myelocyte

Blood Chemistry

	<i>Sugar</i>	<i>Nonprotein nitrogen</i>
6/22/42	148 mg. %	32 mg. %
6/25/42	99 mg. %	
7/1/42	131 mg. %	28 mg. %
7/3/42	159 mg. %	32 mg. %

* Hemoglobin, 14.5 gm.

Additional Tests

- 6/24/42 Kline exclusion test, negative.
7/1/42 Basal metabolic rate, +6 and +7 (two readings). (Patient had a slight fever on this day.)

Necropsy Findings

The post-mortem examination was started about 10 hours after death. The body measured 159 cm. and weighed about 120 lbs. The general configuration was striking. The head, neck and trunk had a puffy appearance due to the massive deposition of subcutaneous fat, but the extremities were thin, the fingers and ankles being slender and delicate. A dusky cyanosis of head and neck, extending down to the clavicles, had persisted. Indurated, papular, acneform lesions were present on the face and anterior part of the body. The eyes were prominent and there was reddening of the conjunctivae. The hirsutism consisted not only of a masculine distribution of the pubic hair, which extended up to and beyond the umbilicus in the midline, but also a growth of coarse, long, yellow-brown hair over the well developed breasts, over the lateral aspects of the abdomen, over the chin and upper part of the neck, and over the upper lip. The hair of the scalp and axillae was abundant. The abdominal striae were irregular purplish bands, 6 or 8 on each side, 4 or 5 mm. wide, extending from the groin to a level somewhat above the umbilicus.

The right pleural cavity contained about 700 cc. of slightly cloudy, yellow fluid containing flecks of fibrin. The *heart* weighed 380 gm. and showed moderate thickening of the wall of the left ventricle. The *lungs* were congested and boggy; each pulmonary artery contained a friable red-brown embolus, and in the right lower lobe a softened, opaque, brownish infarct was encountered. No source was found for the emboli. The *spleen* weighed 150 gm., had a tense capsule and a soft, friable, bulging pulp. Microscopically, there was marked congestion and a rather striking paucity of lymphocytes in both the malpighian corpuscles and the pulp. The *pancreas* weighed 80 gm.; microscopically both the acini and islets were well preserved. The *kidneys* weighed 137 and 185 gm., respectively; they were rather pale and slightly swollen, with no gross evidence of scarring. In the left ureter, at its origin from the pelvis, there was a soft, yellow, crumbling calculus about 2 cm. in diameter. This material did not burn in the flame and dissolved in hydrochloric acid with effervescence, hence was probably chiefly calcium carbonate. Microscopically, the renal tubules were poorly stained and granular, doubtless because of post-mortem change. The large and medium-sized arteries showed no definite

change, but many of the afferent arterioles at their entrance into the glomerular tuft showed a distinct hyaline thickening (Fig. 6). This change was quite diffuse, being found throughout both kidneys. The *uterus* measured 7 by 4 by 3 cm.; it showed a smooth, pink endometrium and firm muscular wall.

Each *ovary* was small (about 2.5 by 1 cm.), hard and yellow-white, like that of a senile woman. In the left was a cyst 1 cm. in diameter containing a clear fluid. Microscopically there were several corpora albicantia but no corpora lutea; a number of primordial follicles were seen, and one questionable graafian follicle. The *thyroid* weighed only 10 gm.; under the microscope the acini varied considerably in size and were lined by a cuboidal epithelium of moderate height, without papillary infolding; colloid was fairly abundant and showed vacuolation. The *parathyroids* did not appear remarkable grossly. The *bones* were cut with unusual ease and showed a sparse trabecular pattern. The *bone marrow* showed a rather marked shift to the left in the granulocyte series, as might be expected from the last blood count. The major *arteries* were almost totally free from atheromatous change. A section of *skin* taken through one of the abdominal striae showed a slight thickening of the epidermis and partial replacement of the dense collagenous tissue of the corium by an accumulation of fairly young fibroblasts arranged parallel to the surface. An elastic tissue stain showed no definite diminution of the elastic fibers. In spite of the purple color seen during life, no abundant vascularity was seen in the section (a similar experience is recorded by MacCallum, Fitcher, Duff and Ellsworth¹). The brain weighed 1300 gm., was symmetrical, and showed no narrowing or flattening of the convolutions. Blocks from the anterior and posterior hypothalamus, frontal cortex, hippocampus, cerebellum and medulla, embedded in celloidin and stained by a modified Nissl's method,* showed no alterations in the ganglion cells or other changes. Sections taken in the vicinity of the infundibulum did not show the proliferation of large vessels described by Globus² in a case of Cushing's syndrome.

The region of the *right adrenal gland* was occupied by a mass of neoplastic tissue weighing 183 gm. The lower portion of this mass was the better preserved part and had a fairly well defined capsule of fibrous tissue. The cut surface was rather soft and of a deep yellowish brown color, with fine streaks of gray. Some of the tissue, near the capsule, was red-blue and boggy. The upper and larger part of the tumor mass was firmly attached to the under surface of the liver and

*The brain tissue was fixed in a 4 per cent solution of formaldehyde, embedded in celloidin and stained with toluidine blue.

had a delicate capsule which was easily ruptured, allowing the escape of markedly autolyzed, soupy, yellow-brown tissue. When the right suprarenal vein was opened, a portion of the tumor was seen to be bulging up beneath the endothelium of the vein. It had not broken through, however, and no metastases were found. A small amount of the right adrenal, showing cortex and medulla, was found attached to the medial border of the tumor mass.

Microscopically, much of the neoplastic tissue was necrotic, and only poorly stained outlines of cells were seen. In the better preserved parts, the cells assumed in places a rather compact arrangement of relatively small cells in sheets or masses separated by large sinusoidal blood vessels (Fig. 1). In such regions there was often a suggestion of a cord-like arrangement but no definite resemblance to any part of the normal adrenal cortex. (Fig. 7, from a large, apparently inactive cortical adenoma discovered at autopsy in another patient, is included for comparison.) In other places the cells had a still more haphazard arrangement and were larger, varying in shape and size, with abundant acidophilic cytoplasm and occasional bizarre giant nuclei (Figs. 2, 3 and 4). Vacuolation of the cytoplasm was not prominent, most of the cells having a granular appearance. Mitotic figures were extremely rare. In a few cells there was a fine yellow-brown pigment. This occurred chiefly in cells surrounding some of the large sinusoids (Fig. 5). It appeared only in the tissue which had been fixed in Zenker's fluid, not in that which was fixed in formaldehyde solution.

In an attempt to decide definitely whether the tumor was of cortical or medullary origin, use was made of the histochemical methods described by Bennett.^{3,4} The results were, unfortunately, equivocal. Some slight darkening of the pigment occurred when the Zenker-fixed sections were "intensified" with sulfanilic acid and with ammoniacal silver. In fact, the darkening seemed as great as that observed in the medulla of control adrenal glands. In the latter, however, the zona reticularis of the cortex also became darker. Thick frozen sections, treated with phenylhydrazine, exactly as described by Bennett,³ to demonstrate ketone bodies, took on a faint yellow color, considerably less than that of control adrenal glands. Similarly, some blackening, again less than that of controls, occurred with Reichstein's³ silver solution. In frozen sections stained with Sudan IV, red-staining material was demonstrated only in a few cells, and these seemed to be in autolyzed portions of the tumor. Likewise, when the sections were examined in polarized light, a few tiny particles of anisotropic material, apparently identical in part with that which stained with Sudan IV, were seen after considerable search. In the medullae of control adrenal

glands, most of which had been fixed within 2 or 3 hours post-mortem, small amounts of Sudan-staining material were seen, but no anisotropic lipoids.

Several sections were stained by the ponceau-fuchsin method of Broster and Vines,⁵ with several normal adrenals and cortical adenomas as controls. Some of the necrotic cells were stained red, but the cytoplasm of the better preserved cells took on a bluish tinge. The results were therefore regarded as negative. Iron hematoxylin stains (Goormaghtigh⁶) were negative, perhaps because of the rather extensive autolysis.

The *left adrenal gland* was found in its usual location. It was not remarkable in general shape, but was unusually thin, weighing only 3.6 gm. Section showed a narrow yellow cortex surrounding a gray, translucent medulla. Microscopically, both cortex and medulla were narrowed. The cortical cells were markedly vacuolated.

The *pituitary gland* measured 14 by 7 by 7 mm. and did not appear unusual in shape. It was fixed in Zenker's formaldehyde solution, embedded in paraffin and cut serially. Many sections were stained with hematoxylin and eosin, a modification of Mallory's acid-fuchsin aniline blue method,⁷ and the Mann stain.⁸ No adenoma was found. However, the majority of the basophile cells, which seemed to be somewhat reduced in number, showed to a striking degree the hyaline change described by Crooke.⁹ Occasionally the basophile granules seemed to be completely replaced by the hyaline material (Fig. 10), but in many of the cells a small clump of granules remained, usually adjacent to the well preserved nucleus (Fig. 9). (For comparison, Fig. 8 is included, showing normal basophile cells, from the same case as Fig. 7.) The acidophile and chromophobe cells were well preserved and the posterior lobe did not appear remarkable.

Urinary Androgens

About 10 cc. of pale urine, recovered from the bladder post-mortem, was sent to Dr. Ralph Dorfman, who found, by a colorimetric method, a value of 130 mg. per liter for total 17-ketosteroids; by the same method the normal values for females range between 7 and 15 mg. per liter.

Assay of Neoplastic Tissue

About 100 gm. of the neoplastic tissue was cut into small pieces, preserved in 95 per cent alcohol and sent to Dr. Dorfman. Having previously failed to find androgens in adrenal tumors, he attempted to demonstrate cortin, but was unable to show any significant quantity, using the cold protection test in adrenalectomized rats.

A few grams of the neoplastic tissue which had been preserved in Klotz solution for several months was ground up and extracted with N/10 hydrochloric acid. When the extract was tested by the method of Folin, Cannon and Denis¹⁰ a blue color appeared which was slightly more intense than that of a control solution of epinephrine (0.0001 per cent). However, the Vulpian, Comessatti, and Ewin's color reactions,¹¹ which were positive with the control solution, were negative when applied to the tumor extract. No attempt at assay on animals was made, since it was felt that the partially necrotic neoplastic tissue would certainly contain pressor substances of nonspecific type.

Post-Mortem Bacteriology

From the pleural fluid, the spleen, and urine *Staphylococcus aureus* and a nonhemolytic streptococcus were grown; from the heart's blood a nonhemolytic streptococcus and *Escherichia coli*.

Anatomical Diagnoses

A. Carcinoma(?) of adrenal gland (right); hirsutism; acne; atrophy of ovaries; hyaline change of Crooke in pituitary basophils; obesity, confined to head, neck and trunk; purple abdominal striae; cyanosis of head and neck; exophthalmos; arteriosclerosis of kidneys; cardiac hypertrophy; osteoporosis; multiple healed fractures of ribs; calculus in left ureter.

B. Pulmonary emboli (source undetermined); pulmonary congestion and edema; pulmonary infarct in right lower lobe; fibrinous pleurisy (right); acute splenic tumor; cloudy swelling of viscera.

DISCUSSION

The accurate histological identification of functioning adrenal tumors would seem to be of major importance in view of the far-reaching clinical conclusions which are being drawn from such cases. At the same time the number of such tumors which are apparently nonfunctioning is striking¹²⁻¹⁴ (*cf.* Fig. 7).

A fairly well defined clinical picture of paroxysmal hypertension is being described with increasing frequency in association with pheochromocytoma, and epinephrine has been demonstrated in some of these tumors.^{15-19b} It is interesting that hyperglycemia^{19c} and "hypermetabolism" may be encountered in such cases and that the episodes of paroxysmal hypertension may resemble hypoglycemic shock.¹⁸ In one of the cases reported by McCullagh and Engel,¹⁸ urinary androgens were found to be within normal limits.

A syndrome of "adrenal virilism" associated with cortical hyper-

plasia or adenoma has been recognized for many years^{16, 20, 21} although sometimes changes in the adrenals are not clearly demonstrated at operation or at necropsy.²² More recently there have been increasingly frequent reports of hypertension (usually not paroxysmal) in association with hyperplasia or tumors of the adrenal cortex.^{23, 24} It is both affirmed^{25, 26} and denied²⁷ that the adrenal cortex is enlarged in cases of essential hypertension.

In Cushing's syndrome the situation is even more complex. As Haymaker and Anderson²⁰ have pointed out, we have passed through a "pituitary epoch" in the study of this disease and are now in the midst of an "adrenal epoch," the general tendency being to interpret the syndrome as a manifestation of hyperfunction of the adrenal cortex.^{16, 28-30} Yet the only constant pathological finding seems to be the hyaline change of Crooke^{9, 31, 32} in the pituitary basophils, which would perhaps suggest that the fundamental disorder, whether "primary," or "secondary" to something else, may lie in the anterior pituitary gland and that the name "pituitary basophilism" may properly be retained (as Crooke and Callow³³ have done) for all these cases.

Since Cushing³⁴⁻³⁶ described the syndrome, a good many cases have been recorded exhibiting a similar group of symptoms. The patient herein described presented practically all of the signs and symptoms which have been mentioned in reported cases of this disease in adult women; *viz.*, amenorrhea, hypertension, hyperglycemia difficult to control with insulin,³⁷ polyphagia,³⁸ obesity confined to head, neck and trunk, the typical "moon face" with cyanosis of head and neck, purple abdominal striae, hirsutism, acne, osteoporosis with multiple fractures,³⁹ renal calculi, feelings of fatigue or apathy, and mental symptoms.⁴⁰ The high urinary androgen excretion and progressive enlargement of the clitoris have been noted particularly in the cases associated with tumors diagnosed as carcinoma of the adrenal cortex.^{33, 41} Death from overwhelming infection is also common. (In this instance the axillary abscess may have given rise to both the septicemia and the pulmonary emboli.) Indeed, the only frequently described clinical finding which was absent in the case here reported was polycythemia. From the anatomical point of view, renal arteriosclerosis^{42, 43} is mentioned fairly frequently and the hyaline change of Crooke⁹ in the pituitary basophils, when looked for, appears to be a constant finding.

Since the Cushing syndrome is the subject of much recent and current discussion,^{16, 20, 21, 28, 29, 33, 38, 41, 44-47} no attempt will be made to review the literature in detail. However, in reading summaries of reported cases, one is struck by what seems to be an outstanding dis-

crepancy; namely, the relative constancy of the clinical symptoms and the variability of the pathological findings (with the exception of Crooke's change in the pituitary gland). The syndrome has been reported in association with basophile adenoma of the pituitary body, with tumors of the thymus, with carcinoma, adenoma, or hyperplasia of the adrenal cortex, with arrhenoblastoma(?),⁴⁸ and finally, without any of these findings.⁴⁹ Almost as remarkable, perhaps, is the apparent fact that any of these tumors or hyperplasias may occur in the absence of the clinical symptom complex.

The tumor in the present case was at first regarded as a carcinoma of the adrenal cortex, and some support seemed to be given this hypothesis by the atrophy of the other adrenal gland. Further study, however, and especially the finding of pigment in some of the cells in the Zenker-fixed tissue but not in formaldehyde-fixed material, cast doubt on the diagnosis. As already noted, histochemical studies were not conclusive, and Dr. Ralph Dorfman was unable to demonstrate significant amounts of cortin in the neoplastic tissue. Therefore the question arose whether the tumor might not be a pheochromocytoma. The likelihood of simultaneous origin from both cortex and medulla seemed remote.

A section of the tumor was shown to Dr. Fred Stewart who felt at first that its appearance and the presence of pigment in the Zenker-fixed tissue suggested a medullary origin. After further study he said that he thought it impossible to be certain that it was not a cortical tumor. A slide was also sent to Dr. Howard T. Karsner, who stated that on an objective basis he would favor a diagnosis of pheochromocytoma, while admitting that because of its cellular character it could conceivably have arisen from the zona reticularis. Dr. Karsner also remarked that he had rarely, if ever, seen a "pure" medullary tumor of the adrenal; *i.e.*, that most of these tumors have components resembling cortical tissue. This he does not take to mean necessarily that the tumors are of mixed cortical and medullary origin, but rather that neoplastic medullary cells may come to resemble cortical cells morphologically.⁵⁰

Through the courtesy of Dr. Louise Eisenhardt, I had the opportunity of examining slides from four reported cases of adrenal tumors associated with Cushing's syndrome. Two were similar to the present case, showing sheets of cells, most of them with abundant, acidophilic, granular, slightly vacuolated cytoplasm, separated by large sinusoidal blood vessels, but without definite pigmentation. (It was not known whether these tissues were fixed in chromate solutions.) Another showed a cord-like arrangement of "foamy" cells with numerous mitotic figures. Still another contained markedly vacuolated cells,

reproducing, rather faithfully, layers of the adrenal cortex, like the adenoma shown in Figure 7. These slides were also shown to Dr. Stewart, who thought that two of them could possibly be of medullary origin.

Thus it is evident that the histological diagnosis in the case here reported, and perhaps in some others as well, was a matter of considerable difficulty. In this connection some discrepancies in the literature may be noted also. For example, in the case of Porter and Porter,⁵¹ an adrenal tumor, removed in a case of paroxysmal hypertension with, apparently, no other outstanding symptoms, was called a cortical adenocarcinoma by Ewing, who also stated that it contained no pigment. No statement was made regarding fixation in chrome salts. In describing a case of chromaffin cell tumor associated with paroxysmal hypertension, Coller, Field and Durant⁵² stated that such tumors may so closely resemble cortical tumors that the diagnosis must be questioned if chromate fixation is not used. Cragg⁵³ cast doubt on the relation of the chromaffin substance to epinephrine. The situation is hardly clarified by the statement of Geschickter,⁵⁴ in describing benign cortical tumors, that "deposits of chromaffin (*sic*) pigment are common."

Of particular interest is the case recently reported by Neff, Tice, Walker and Ockerblad⁵⁵ of an adrenal tumor in a female infant in whom symptoms began at 8 months with onset of hirsutism, acne, hypertrophy of the genitalia, and, to judge from their illustrations, a puffy obesity of the face. The child had hypertension which is said to have been paroxysmal. Amelioration of symptoms occurred following removal of the tumor, which contained vacuolated, fat-containing cells and "brown granules were seen in many of the cells when the tissue was treated with chrome salts; silver impregnation permitted a diagnosis of chromaffinoma or pheochromocytoma." Although this case cannot be regarded as showing a full-blown Cushing's syndrome, the histology of the tumor seems remarkable when the symptoms are considered. The authors' suggestion that the tumor caused dysfunction of the cortical cells by pressure is not convincing.

Some of the adrenal tumors encountered in cases of Cushing's syndrome have been said to reproduce the structure of the zona reticularis of the normal adrenal, and such an appearance has been linked with the hypothetical "androgenic zone" of the fetal adrenal. The chief proponents of this point of view in the past have been Grollman⁵⁶ and Broster.^{5, 57, 58} More recently Gersh and Grollman⁵⁹ seem to have abandoned Grollman's original position concerning the production of androgens by the adrenal cortex and, in fact, go so far as to suggest that

the androgenic effects seen in pathological conditions may be due to misplaced testicular tissue in the adrenal. Others have questioned the androgenic function of the so-called "x-zone."⁶⁰ Related to the concept of the androgenic zone is the use of the ponceau-fuchsin stain of Broster and Vines.⁵ This is supposed to stain the cytoplasm of the androgenic cells a brilliant red. As previously noted, this stain was negative in the present case. The failure to secure a positive fuchsinophile reaction in my case may have been due to post-mortem change in the tissue. However, the specificity of the stain seems open to serious question.^{3, 12, 14, 49, 50, 61, 62} The siderophile granules described by Goormaghtigh⁶ in masculinizing adrenal tumors were also looked for in the present case and were not found, again possibly because of post-mortem autolysis.

The presence of lipoids, or at least of vacuolation in the tumor cells, is commonly mentioned in the literature on cortical tumors, and it is stated by Cahill, Melicow and Darby¹² that the tumors in their series which were associated clinically with symptoms suggestive of Cushing's syndrome contained more vacuoles than the others. In my case, frozen sections stained with Sudan IV showed positive staining only in areas which appeared to be necrotic. Frozen sections were also examined in polarized light, both with and without treatment with digitonin,³ and negligible amounts of anisotropic lipoids were seen. In this connection, it should be remarked that fat vacuoles have been mentioned, though rarely, in reported cases of pheochromocytoma,⁵⁵ as well as in tumors of the carotid body⁶³ (*cf.* also the statement of Karsner,⁵⁰ cited previously). Also, it must be remarked that wide fluctuations, including extreme depletion, may occur in the amount of fat in the cortex of normal adrenal glands under various physiological and pathological conditions.^{20, 64, 65} It is reasonable to suppose that the fat content of tumors may vary in a similar way.

The presence of brown pigment in the cells after chromate fixation has perhaps been given greatest weight as a differential criterion between cortical and medullary tumors. However, even this may be inconclusive, since the zona reticularis of the normal adrenal cortex contains yellow-brown pigment granules, of uncertain nature, and these may appear in cortical adenomas. Conceivably, of course, the distribution of pigment in a tumor may be so uneven that it may appear in some sections and not in others.

In regard to the general cyto-architecture of adrenal tumors, it is generally stated that the cells of cortical tumors are likely to be arranged in cords, imitating more or less the normal cortex, while in the pheochromocytoma the cells are usually said to be arranged in sheets

or nests, to be polyhedral, with rather abundant cytoplasm, and to vary considerably in size and shape, with occasional giant forms.^{12, 15, 19b, 66, 67} But Wu,⁶⁸ in a review of carcinoma of the adrenal cortex, emphasized the frequency of "pleomorphism" of cells.

It is usually said that cortical tumors are rarely malignant, and pheochromocytomas apparently metastasize only in exceptional cases. The tumor in the case here reported was not definitely malignant, although there was a suggestion of an invasive tendency in the nodule protruding beneath the endothelium of the suprarenal vein.

Additional evidence of the complexity of the situation with regard to functioning adrenal tumors is the apparent fact that the cortical origin of all of the so-called cortical hormones, while extremely likely, is not established beyond all question. In the recent review of the cortical hormones by Reichstein and Shoppee⁶⁹ the following statement appears: "In recent years whole glands rather than the dissected cortices have been used almost exclusively as starting material; this is also the case for the industrial preparation of the extracts used in clinical work. Nevertheless, it is highly probable that the steroids originate from the cortex and not from the medulla." (Reference is then made to the histochemical work of Bennett, cited previously.)

Kendall⁷⁰ stated that, although he has never tried to recover cortical hormones from a pheochromocytoma, he is "quite certain" that cortical hormones are not produced by medullary tissue.

Some of the differential histological criteria may be summarized as follows: in favor of a cortical tumor are (1) cord-like arrangement of cells, (2) fat vacuoles in cells, (3) absence of brown pigment after fixation in chromate solutions or other oxidizing agents.* In favor of a medullary tumor, on the other hand, there may be considered: (1) polyhedral cells, varying in size and shape, arranged in sheets or nests; (2) absence of fat in tumor cells; (3) presence of pigment after chromate fixation. It is obvious, however, that in some cases, such as the one here reported, the application of these criteria may not result in a clear-cut answer (*cf.* also Coller, Field and Durant⁵²).

Finally, in view of the evident difficulties of deciding in some cases whether an adrenal tumor is of cortical or medullary origin, and the general uncertainty regarding the functions of such tumors, it may be suggested that future cases, especially when associated with Cushing's syndrome, be carefully studied by histochemical methods and by prompt assay of the fresh neoplastic tissue for both epinephrine and

* Bennett⁴ pointed out that the term "chromaffin" is a misnomer, since the brown pigment is not a chromium compound, but the product of oxidation of epinephrine or related substances and can be obtained by the use of other oxidizing agents.

steroid hormones. Information gained in this way should be of more value than that derived from simple inspection of paraffin sections, and should permit better correlation with the clinical findings.

SUMMARY

A case of Cushing's syndrome associated with an adrenal tumor of uncertain histogenesis, possibly a pheochromocytoma, is described. A high content of 17-ketosteroids was found in a single sample of post-mortem urine, but no significant amount of cortin was demonstrated in the neoplastic tissue.

Application of the usual histological criteria as well as more refined technics did not yield a clear-cut answer as to the origin of this neoplasm. Careful study by histochemical methods and by assay of fresh tissue for epinephrine and steroid hormones may be expected to give more definite information than routine histological methods in the investigation of adrenal tumors associated with Cushing's syndrome.

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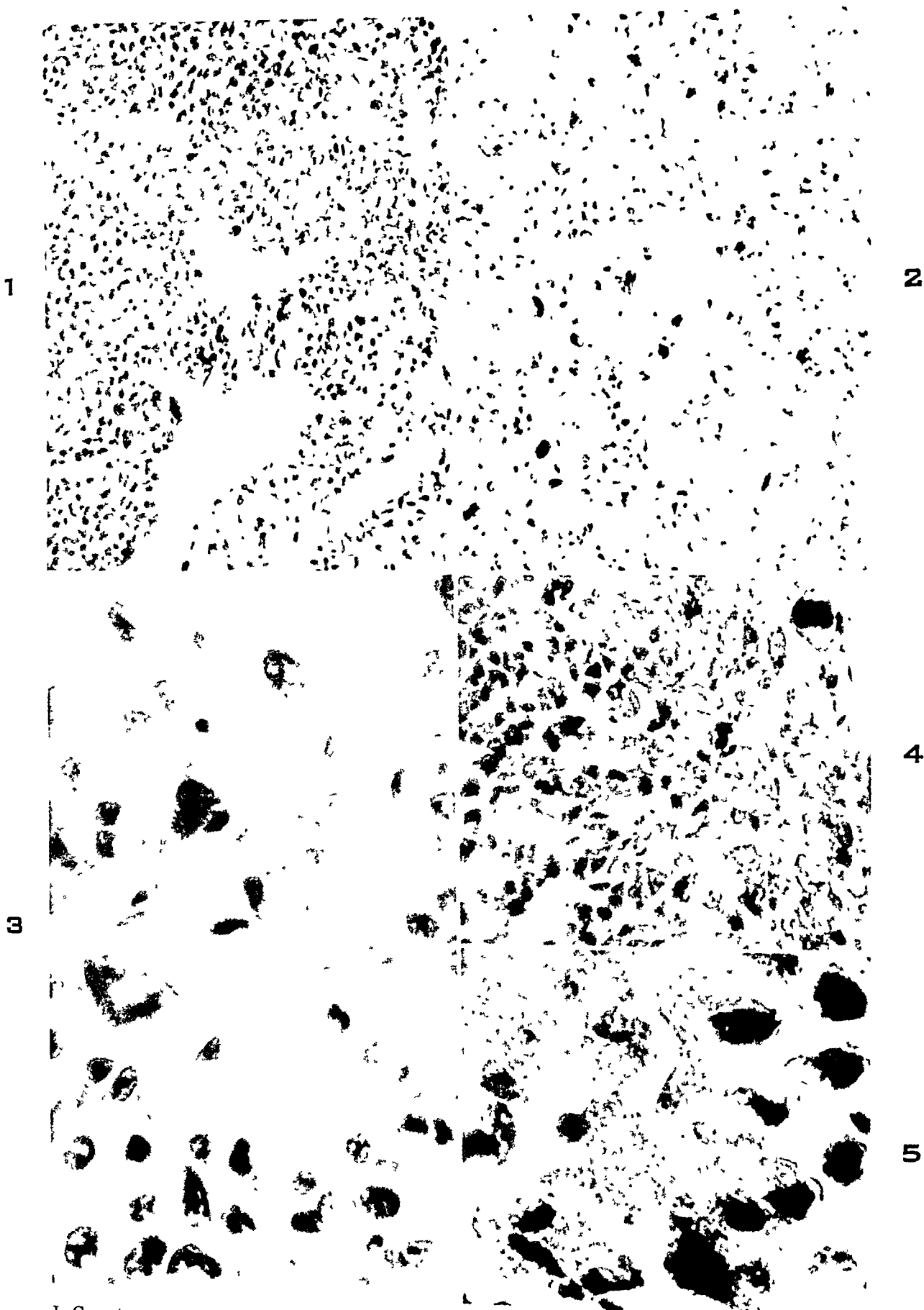
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DESCRIPTION OF PLATES

PLATE 135

- FIG. 1. A part of the adrenal tumor in which the cells are relatively small and arranged in compact sheets surrounding large sinusoids. Hematoxylin and eosin stain. $\times 200$.
- FIG. 2. Another portion of the tumor, showing a quite different structure. The size of the cells may be compared with those in Figure 1, which is taken at the same magnification. Hematoxylin and eosin stain. $\times 200$.
- FIG. 3. Higher magnification of cells from a field similar to that in Figure 2, to show variation in size and shape. One or two cells appear to have small vacuoles in the cytoplasm. Hematoxylin and eosin stain. $\times 700$.
- FIG. 4. Another field, showing hyperchromatic nuclei and deeply staining cytoplasm. A tumor giant cell is seen in one corner. Hematoxylin and eosin stain. $\times 350$.
- FIG. 5. A group of pigmented cells adjacent to a sinusoid. In the original preparation the cytoplasm of these cells has a diffuse yellow-brown color. Hematoxylin and eosin stain. $\times 750$.



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Cushing's Syndrome and Pheochromocytoma

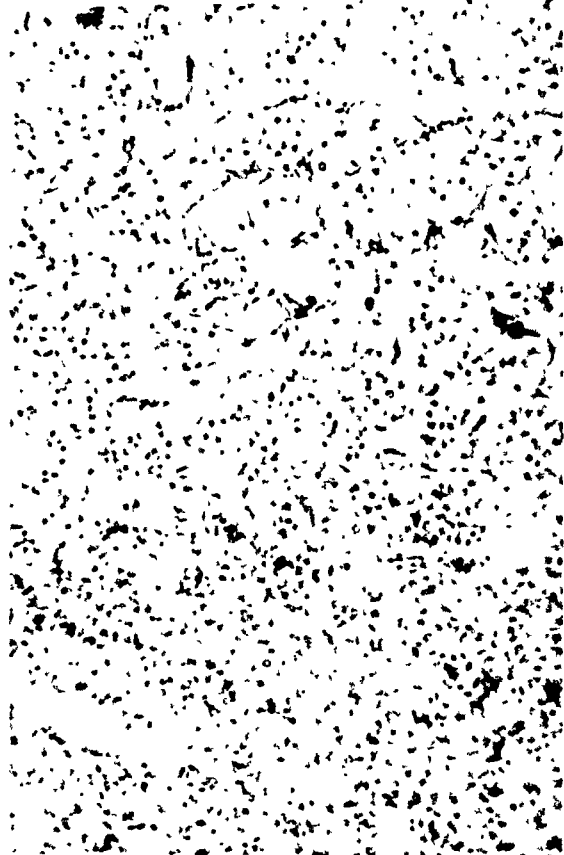
PLATE 136

- FIG. 6. Hyaline thickening of afferent arteriole in kidney. Hematoxylin and eosin stain. $\times 335$.
- FIG. 7. Representative field from an apparently nonfunctioning cortical adenoma about 3 cm. in diameter, encountered unexpectedly at autopsy in an elderly woman. This is for comparison with sections of the tumor in Plate 135. Hematoxylin and eosin stain. $\times 125$.
- FIG. 8. Normal basophile cells, from the same case as Figure 7, for comparison with Figures 9 and 10. The cell near the center with large, eccentric nucleus is an eosinophil. Mann stain. $\times 1600$.
- FIG. 9. Two basophile cells from the pituitary gland of the case reported, to show hyaline change of Crooke. The granules are partly replaced by hyaline material. Mann stain. $\times 1600$.
- FIG. 10. Two more basophile cells, one a very large one, from the pituitary gland of the case reported. The granules have been almost completely replaced by hyaline material. For comparison with Figure 8. Mann stain. $\times 1600$.

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KERATODERMIA BLENNORRHAGICUM

REPORT OF CASE WITH AUTOPSY *

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Although gonorrhea is still one of the most common infectious diseases, the general systemic form, keratoderma blennorrhagicum or gonorrheal keratosis, is one of the very rare causes of death. While the disease is known to be a general systemic one, with the most striking local manifestations in skin and joints, most studies have been limited to biopsies of the skin and clinical observations. Only a small amount of experimental work has been done and, because the disease is seldom fatal, complete autopsy reports and anatomical studies are singularly deficient in the literature.

A review of the literature reveals reports of only five fatal cases of gonorrheal keratosis, and of these only three include the results of autopsy. The fatal case of Lees and Percival,¹ and one of the two fatal cases of Rost² were apparently not studied by necropsy. The other case reported by Rost is imperfect because this patient was never known to have had gonorrhea. However, a typical history of arthritis, preceding by 1 year a pustular and later hyperkeratotic lesion of the skin, makes the clinical diagnosis credible.

In the three cases corroborated by anatomical studies, most of the essentials have been found. In Rost's² second case the post-mortem examination showed a small heart, generalized muscle atrophy, slight thickening of the tricuspid valve and early arteriosclerosis, particularly marked in the aorta and kidneys. The testicles were small, but otherwise normal in appearance, and there was a generalized bony ankylosis. Simpson³ found in his case localized fibrinous pericarditis and some fibrous adhesions from the spleen to the diaphragm. There was chronic prostatitis, seminal vesiculitis, testicular atrophy together with a generalized deforming polyarthritis and passive congestion of the viscera. Simpson made bacterial studies of the prostate, seminal vesicles and joint fluid, but found no gonococci. Scholtz⁴ found involvement of the serous membranes, but no fibrinous exudate on serous surfaces. There were general serous effusions, however, the largest being 150 cc. of fluid in the pericardial cavity. He found also early bronchopneumonia, an hyperplastic spleen and a very active bone marrow. The synovial surfaces of the various joints were examined in his case and, although

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there was a generalized partial ankylosis, the synovial surfaces were smooth and showed no adhesions or fibrinoid deposits. The ankylosis was in a position of semiflexion. No fluid was found in any of the joints. The skin lesions in this report are designated as extremely numerous and generalized.

All of these cases with fatal termination have been those of males who have had an unusually persistent, resistant and generalized arthritis with deformities, and they have all shown generalized skin lesions. Excepting the case reported by Simpson,³ the disease has terminated with a bronchopneumonia and marked emaciation. These cases, in common with nonfatal cases, pass usually through a stage of fever, toxemia and debility, but among the nonfatal cases reported only 2.7 per cent have had generalized skin lesions. Because of the rarely fatal termination of this form of gonorrhea, complicated by typical skin changes and a generalized ankylosing arthritis, we wish to report a case of keratoderma blennorrhagicum with autopsy.

REPORT OF CASE

R. P. H., a white, male laborer, first developed typical acute gonorrheal urethritis in 1929, at the age of 20. Three weeks later he began to show the signs and symptoms of acute arthritis of one knee, with swelling, heat, tenderness and restricted motion. The inflammatory process appeared serially in all of the larger joints of the body, and the patient was hospitalized for 8 months, during which time there was continual involvement of at least one or two joints. He was then discharged but continued to have moderate symptoms for 2 years and was not completely well until after an appendectomy was performed in 1932. From 1932 until 1940, the patient was symptomatically well.

In March of 1940, at the age of 31, there was a recurrence of acute arthritis which again involved every joint which had been involved previously, and also some of the smaller joints. He entered the San Francisco Hospital on June 12, 1940, at which time the joints involved were the left sternoclavicular, the left fourth metacarpophalangeal, the right third metacarpophalangeal, several metatarsal joints in both feet, and the right elbow. He was given a course of six pyrotherapy treatments, with considerable improvement, and was discharged to the Clinic service. At this time he was having a morning urethral discharge of a few drops, but several examinations failed to show gonococci. There was also atrophy of the right testicle, and enlargement of the inguinal lymph nodes. A cutaneous Frei test was negative. The skin was dry and scaly, with an acne-like eruption upon the trunk, and at this time a diagnosis of seborrheic dermatitis was made.

The patient then went to Des Moines, Iowa, believing that the warmer climate would help his arthritis. Instead he had a relapse. He was in the Des Moines Army Hospital for 5 months, during which time he received a "complete course" of sulfanilamide and sulfathiazole.

Aside from a small patch of dry, scaly skin upon the scalp for 2 years previously, the major skin lesion appeared while the patient was hospitalized in Iowa. It was described as a nonpruritic rash, believed to have started as patches upon the extensor surfaces of knees, elbows and shoulders, but spreading over the entire body. The lesion appeared before sulfa drugs were given, and there is no history of medication with bromides, barbiturates, iodides, or other drugs capable of producing dermatitis of this type.

He re-entered the San Francisco Hospital on December 23, 1941, with an acute relapse of arthritis and persistent dermatitis.

Physical Examination. Examination at this time showed an acute arthritis of the ankles, with a less acute involvement of the knees (which were still tender), moderate involvement of the elbow and shoulder joints, and some deformities of the metacarpophalangeal joints in the hands. There was generalized muscle atrophy and cachexia. There were several carious teeth. The blood pressure was 110/70, and the remainder of the general examination revealed nothing abnormal.

The skin showed a generalized papular eruption consisting of discrete but often coalescent, ragged, crusted lesions. On the trunk they were rupial and resembled shallow cones, with a grayish tan or brown color. They ranged from 3 to 15 mm. in diameter, and were so numerous that in most places they were almost contiguous. On the extremities, especially on the plantar and palmar surfaces, the lesions were often coalescent to form large, irregular, wandering, elevated patches of cornified, crusted material. Lesions on the dorsum of the hands and on the scalp were considerably smaller but just as numerous and were pale, yellowish gray and of a smoother contour than the larger ones seen elsewhere. A few of them resembled "droplets of wax." These lesions were the more easily removed and beneath them the skin was moist, slightly reddened, and level with the surrounding skin. The lesions were most numerous upon the trunk and tended to avoid the body folds and also the areas of skin in contact with the bed. In the groins and axillae, and to a lesser degree in the other body folds, the skin was moist and reddened and showed numerous white areas which were slightly elevated and somewhat macerated. The nails were thickened, white and scaling. There were decubital ulcers on the heels and over the sacrum and midportion of the back.

Laboratory Findings. The hemoglobin was 65 per cent, the red blood cell count was 2,800,000 and the white blood cell count 9,200 per cmm., with a normal smear and differential count. Urine and stool were normal. Wassermann and Kahn tests of the blood were negative.

Therapy. The patient was treated with potassium permanganate baths, vitamin A and cod liver oil. The arthritis continued unabated, and the temperature ranged from 100° to 102° F. The patient was in extreme distress almost continually and required increasing doses of morphine. He gradually became cachectic, had a persistent toxemia and finally developed bronchopneumonia and expired. The skin lesions had failed to respond to any type of local therapy.

Necropsy

The autopsy on January 8, 1942, showed an extreme degree of emaciation and generalized, partial ankylosis with restricted mobility of the joints, with the more noticeable deformity in the hands and wrists. There was marked edema and some reddening of the ankles, which were still warm at the time of autopsy. The skin showed essentially the lesions described clinically.

Upon opening the body the peritoneal and pericardial cavities were without adhesions or exudate, while the pleural cavities showed only a few old fibrous adhesions. There were no effusions.

The lungs were edematous and showed areas of consolidation about the bronchi with numerous focal abscesses in each lower lobe.

The prostate weighed about 30 gm., was homogeneous in consistency, and a little more dense than normal. The right testicle was rather

small, but showed no inflammation or fibrosis. The aorta showed a few small atheromatous plaques in its abdominal portion, but no evidence of lues. In the right ankle joint small fibrous adhesions crossed the joint cavity in several places, with thickening and fibrosis of the synovial membrane, while other synovial membranes were clean and smooth. There was no effusion into this, of other joints, although there was edema around the right ankle. The heart, liver, spleen, pancreas, stomach and intestines, kidneys, ureters, bladder, adrenals, thyroid gland, pituitary body and brain showed no gross pathological changes.

Microscopic Examination. Sections of the skin lesions showed all of the changes described in detail by Keim⁵ and re-emphasized by numerous writers, except for vesiculation.

The earliest change has not been a constant finding of the various writers and might not be expected when the disease was sufficiently advanced to cause death. The earliest lesion (Fig. 1) is a tiny collection of polymorphonuclear leukocytes in the stratum granulosum of the skin with elevation of the stratum lucidum to form a little nest. The prickle cell layer is not involved at this time. As the process advances, the corium begins to show infiltration of lymphocytes and some edema of the dermal papillae. The lymphocytic invasion is restricted to the superficial layer of corium and is rarely found deeper or in the subcutaneous tissue. It persists throughout the life of the lesion. A few plasma cells also may be found, but in the progressing lesions only rarely are there any polymorphonuclear leukocytes. Later the superficial pustules gradually become larger, further elevating the keratinized layer, and soon produce a noticeable depression of the prickle cell layer, but the lesion is still very well circumscribed (Fig. 2). This pustule now shows various degrees of keratinization, forming a smooth, rather opaque, pale-staining mass which fuses with, and becomes indistinguishable from, the old stratum lucidum. Meanwhile a new stratum lucidum has begun to form beneath this keratinizing mass of polymorphonuclear cells, and can be seen extending in from the edges toward the center (Fig. 3). This new stratum lucidum is obviously formed by keratinization of the superficial layer of prickle cells in contact with the pustular mass. It soon becomes complete, forming a dimple in the intact skin with the superficial lesions still forming a conical elevation at the same spot. The keratinizing process is now complete; no new cells infiltrate the lesion, and the mass soon becomes almost homogeneous except for a few multilobed nuclei scattered through it. The underlying skin at this point gradually flattens out so that the keratinized mass is quite definitely elevated, and the under-

lying skin is level with the surrounding normal skin. The skin is now intact, with lymphocytes in the corium and with a large squamous crust upon the surface. At this point the crust may desquamate, leaving unscarred, normal skin (Fig. 4), or a new lesion, developing at this time or just prior to it, may be ripening and may produce another layer of crusting. This repetitious process eventually produces the characteristic large, irregular, horny lesions seen upon the extremities.

The exemplary lesion just described was the typical one upon the scalp, where the lesions were fairly smooth and discrete and did not show brownish coloration. Acanthosis was either very slight or only moderate in amount, never exceeding the degree seen in Figure 5. Parakeratosis was observed to a very limited degree in the early lesion. It is possible that it is only simulated by separation of layers of keratinizing material, without an actual absolute increase in the amount of the stratum lucidum. The prickle cell layer, basal layer, and subcutaneous tissue showed no evidence of involvement.

Occasionally a mild endarteritis of medium and small-sized arteries in the subcutaneous tissue was found. These arteries showed swelling and irregularity of the endothelium, and slight subintimal fibrosis. There was no other evidence of reaction at this level.

Bacterial stains of these sections have failed to demonstrate organisms in either the lesions or the surrounding skin.

Section of tarsal joints in the right ankle showed a few small adhesions bridging the synovial membranes, with considerable fibrosis around them and with several dense cordons of lymphocytes and plasma cells in the adjacent collagen (Fig. 6). There was a mild chronic prostatitis and a subacute posterior urethritis. No bacteria were found in these fixed tissues. Sections of skeletal muscle showed diminution in diameter of the muscle fibers and an apparent or relative increase in the number of nuclei of the sarcolemma, the capillaries and the endothelial cells (Fig. 7). No inflammatory infiltration was seen. There was an unusually large number of macrophages, filled with yellowish brown pigment giving a positive reaction for iron, in the lymph nodes of the hilar and abdominal region, in the gastric mucosa, the bone marrow, spleen, liver, the inflamed portion of the ankle joints and in the posterior lobe of the pituitary gland. A moderate amount of iron pigment was seen in the spleen. In the liver there was considerable fatty infiltration and mild congestion. There was a well developed, confluent bronchopneumonia, and in the right testicle the seminiferous tubules showed atrophy and were separated by diffuse fibrosis. The bone marrow was active. Sections of the other organs were normal. Unfortunately, culture of the blood was not done.

DISCUSSION

The history and skin lesions in this case are consistent with keratoderma blennorrhagicum, although the skin lesions persisted over a long period. Since the original arthritis preceded the dermatitis by about 10 years, we may consider psoriasis arthropathica to be extremely unlikely. Of the other criteria set up by Epstein⁶ for the differential diagnosis of these two diseases, almost every one points toward gonorrheal keratosis.

The course of this case was similar to that of the other fatal cases, with a generalized eruption, marked emaciation, exhaustion, persistent fever and, finally, bronchopneumonia. The ankylosis was not so well developed as in some of the reported cases, and the arthritis was less active. Prostatitis, urethritis and testicular atrophy are all part of the inflammatory process of the genital tract, and are familiar observations in this disease. Testicular atrophy is the most characteristic of these changes. The other findings were all consistent with a state of starvation and chronic toxemia. The distribution of pigment may indicate a general, slow hemolysis, accompanying toxemia and producing anemia. The absence of bacteria in the tissues is in accord with the majority of previous reports.

Although generalized dermatitis indicates a poor prognosis in keratoderma blennorrhagicum, we still wish to emphasize two facts in regard to therapy. One is the failure of sulfanilamide and sulfathiazole to alter appreciably the course of the disease, although administered in large doses during an arthrocutaneous relapse, to a person not previously treated with these drugs. The other point is the appearance of skin lesions following a series of pyrotherapy treatments (to 104° F.) for the arthritis, in spite of the strong recommendation⁷ of pyrotherapy as a treatment for the dermatitis itself.

SUMMARY

Necropsy of a patient with keratoderma blennorrhagicum showed generalized chronic arthritis with a few adhesions in the joints, typical lesions of the skin in varying stages which permitted study of their evolution, chronic prostatitis, chronic posterior urethritis, testicular atrophy, fatty infiltration of the liver, and cachexia. Bacteria could not be demonstrated in sections of the skin. There were no new findings which might help in explaining the cause of this disease.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 137

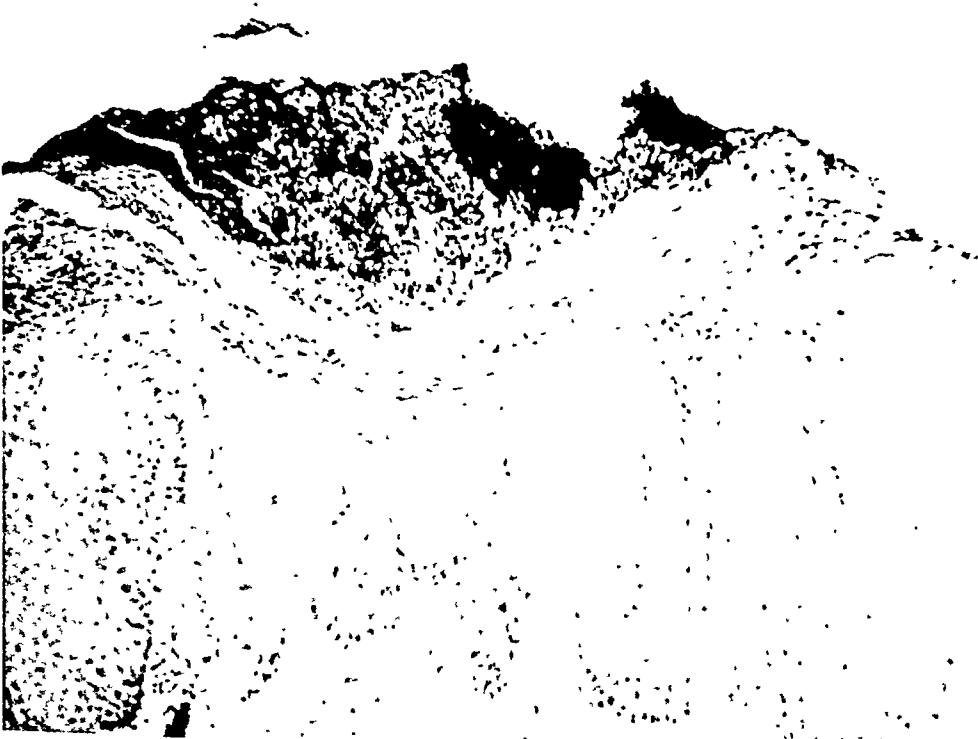
- FIG. 1. Earliest lesion seen, with pustule beneath the stratum corneum and lymphocytes in corium. $\times 145$.
- FIG. 2. Larger pustule than that shown in Figure 1, with cellular débris fusing and hyalinizing. $\times 95$.
- FIG. 3. Pustule a little older than that shown in Figure 2, with new corneal layer separating the older exudate and cellular débris from the prickly cell layer. $\times 120$.



1



2



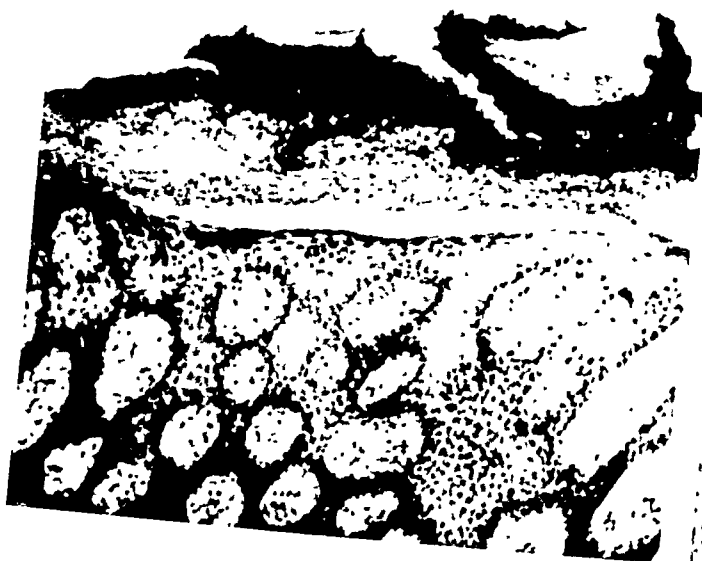
3

Carr and Friedman

Keratoderma Blennorrhagicum

PLATE 138

- FIG. 4. Former pustule, now a squamate crust, separating from the intact skin beneath, which is now level with the surrounding skin. There is an older pustule on the right, with moderate squamate transition, which is being elevated by the newer pustule on the left. Parakeratosis is present in this area. $\times 90$.
- FIG. 5. Early pustule, showing greatest degree of acanthosis seen. No parakeratosis is evident. $\times 93$.
- FIG. 6. Left ankle joint with active synovitis, adhesions and lymphocytic infiltration. $\times 140$.
- FIG. 7. Psoas muscle. Proliferation of endothelial and sarcolemmic cells. $\times 140$.



4

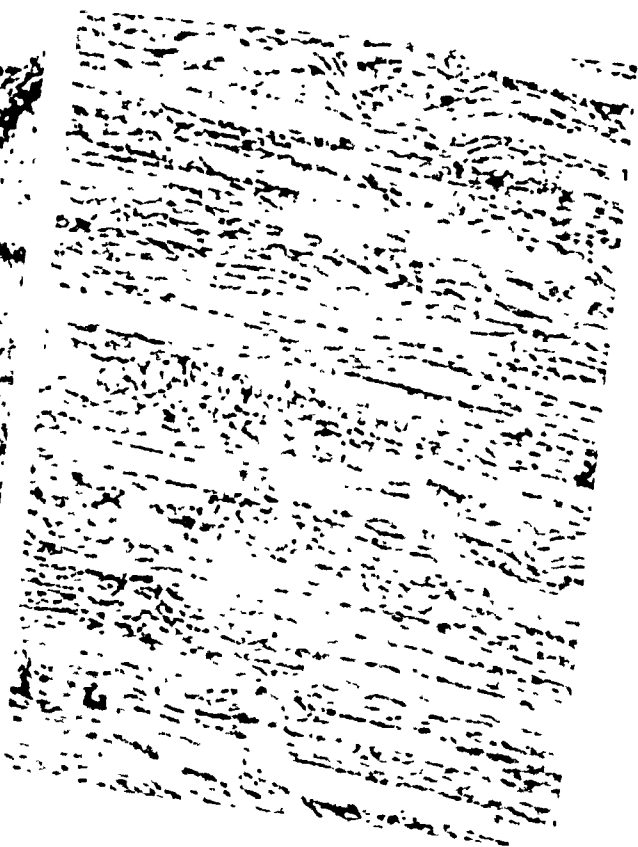


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Keratoderma Blennorrhagicum

PERIARTERITIS NODOSA IN EXPERIMENTAL HYPERTENSIVE RATS AND DOGS*

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In the course of a procedure to test the effect of certain renal extracts upon experimentally produced hypertension in rats and dogs, it was discovered at autopsy that many of the animals had periarteritis nodosa. The lesions found in these animals appeared to be identical in gross and microscopic morphology and in distribution with those of human periarteritis nodosa. A study of this condition in these animals was begun with the hope that it would add to our knowledge of the occurrence of similar lesions in man.

LITERATURE

A summary of the reported occurrence of periarteritis nodosa in animals is presented in Table I, inspection of which reveals that the disease has been found in a wide variety of animals, including cows, pigs, deer, dogs, rabbits and rats. Spontaneous occurrence of isolated cases in animals has been recognized for many years. Wilens and Sproul found many cases in very old rats fed a special diet.

Periarteritis nodosa has been described recently in rats in which hypertension was produced either by placing a silver clamp on one renal artery (Wilson and Byrom), or by wrapping one kidney with cellophane (Friedman, Jarman and Klemperer), or by various other operative procedures to induce hypertension (Cromartie).

Only 3 cases of periarteritis have been described in hypertensive dogs. Child reported its occurrence in 1 hypertensive dog following production of an Eck fistula. Goldblatt † states that he has found the disease in only 2 of more than 1000 dogs examined, while Graef and Page did not mention its occurrence following the production of hypertension by cellophane perinephritis.

No reports have been found of the occurrence of periarteritis nodosa in animals in which the blood pressures were proved to be normal, or in which the kidneys were proved to be free from pathologic change.

METHODS

Clinical and pathological studies were made on 100 rats and 8 dogs used for routine assays of the blood-pressure-lowering activity of cer-

* Received for publication, August 30, 1943.

† Personal communication

TABLE I
Reported Occurrence of *Periarteritis Nodosa* in Animals

Animal	Author	Year	Arteries involved	Remarks
Calf	Guldner	1915	Heart, skeletal muscles	Spontaneous occurrence in a 4-weeks-old animal
Cow	Nieberle	1928	Heart, kidney, liver, spleen, lymph nodes, udder, gall-bladder	Spontaneous occurrence in a 3½-year-old animal
Deer	Lüpke and Jaeger	1906 and 1909	Abdomen, heart, vasa vasorum	This disease appeared in a herd of 100 10-year-old axis deer, born and living in a park in Ludwigsburg; the etiologic factor was thought to be bacterial but attempts to isolate organisms were unsuccessful; the disease was not found in other similar herds in Calcutta and Hamburg.
	Baló	1924	Heart	Spontaneous occurrence in a 4-year-old male fox terrier, which had acute gastritis, parenchymatous nephritis and chronic mitral endocarditis
Dogs	Child	1938	Widespread, especially in heart and mesentery	One of 12 dogs with experimental hypertension produced by constricting renal artery; in this animal an Eck fistula, produced after hypertension was maintained for 6 months, was followed by a slow rise to 300 mm. Hg, ending in hemiparesis and death
	Goldblatt	1941*	"Most manifest in the heart"	Occurrence in 2 of more than 1000 dogs examined; both were hypertensive with uremia
Pigs	Joest and Harzer	1921	Heart, kidney	Spontaneous occurrence in a 12-month-old animal which was lame and had pseudomembranous inflammation in the mouth and throat
	Collins and Goldie	1940	Heart, kidneys, mesentery, synovial membranes	Occurred in 5 of a group of animals given <i>Erysipelothrix rhusiopathiae</i> to produce arthritis; absent in controls and in those injected with streptococci
Rabbits	Harris and Friedrichs	1922	Lung, liver, heart, kidneys	Authors made an emulsion from kidneys of a typical human case of periarteritis nodosa, injected it into ear veins of rabbits which then developed suggestive lesions; emulsions of their involved organs were passed through Berkefeld filter and the filtrate injected into the ear vein of another rabbit which subsequently presented "typical lesions"

Wilson and Pickering	1938	Intestines, stomach, supra-renal gland, liver, heart, eye	Experimental hypertension produced by constricting renal arteries with silver clamps; lesions described as periarteritis nodosa, but not so designated; lesions seemed to be related to rapidly developing severe hypertension
Rich and Gregory	1943	Widespread	Lesions occurred in 12 of 14 rabbits in which hypersensitivity to horse serum was induced experimentally; controls were not described; 10 of the 14 rabbits had acute diffuse glomerulonephritis; blood pressure studies were not reported
Metz	1931	Kidneys, lungs, heart, brain, liver, skin, skeletal muscle	Lesions occurred in white rats following injections of <i>Streptococcus hemolyticus</i> , sterile toxin and nonspecific protein antigen, to which, respectively, the animals had been highly sensitized
Masugi	1935	Kidneys, intestines, lungs, heart, aorta	Lesions occurred in rats which had been injected with rabbit anti-rat-kidney serum.
ilens and Sproul	1938	Widespread	Lesions found in 47, or 9.7%, of a large series of rats studied for cardiovascular disease; these animals were old rats used in a dietary experiment, in which the diet consisted of dried milk and ground wheat; suppurative lesions were common; younger rats on meat and vegetable diet did not develop the lesions
Ham	1940 1941*	Mesentery and spleen	Lesions occurred in animals given a single massive dose of activated ergosterol which caused calcification in the kidneys, which in turn was thought by the author to have led to renal ischemia, hypertension and then periarteritis nodosa
Wilson and Byrom	1941	Most marked in mesentery	Lesions occurred in 28 rats made hypertensive by placing a clamp on one renal artery; animals were well below the age limit of those used by Wilens and Sproul
Friedman, Jarman and Klempner	1941	Pancreas, mesentery, intestines, heart, testes and unwrapped kidney	Lesions described as periarteritis nodosa but not so designated; hypertension produced by cellophane-perinephritic method, using one kidney; inflammatory necrotizing arterial lesions in animals having rapid, severe rise in blood pressure
Cromartie	1943	Widespread	Typical lesions were found in 15 of 37 rats in which hypertension had been produced by various operative methods; 12 of the 15 were infected; another 12 were infected but showed no periarteritis nodosa

Rats

* Personal communication.

tain kidney extracts. The dogs and rats were housed in laboratories in different buildings. The rats were fed Rockland Rat Diet, while the diet for the dogs consisted of dog biscuits, cooked meat scraps and bones, and occasionally milk.

Autopsies were performed on all of these animals and microscopic sections of heart, liver, spleen, kidney, pancreas, mesentery and occasionally other organs and tissues were studied.

Hypertension was induced in the rats by wrapping both kidneys with silk according to the technic described by Kempf and Page. Healthy rats of either sex, all under 6 months of age and weighing 150 to 200 gm., were used. The procedure of wrapping the kidneys was carried out in two stages: one kidney was wrapped with silk and 7 to 10 days later the other kidney was wrapped in similar fashion. Although the silk was autoclaved and the instruments soaked in alcohol, no special additional aseptic precautions were employed. Both stages of the operation were done under ether anesthesia, and the incisions closed with skin clips.

In rats, systolic arterial blood pressure determinations were carried out according to the indirect method of Williams, Harrison and Grollman. The blood pressure readings reported represent triplicate determinations after the animals had been heated in a box at 60° C. for 5 minutes. Blood pressure determinations were made usually three or more times a week.

Arterial blood pressure determinations in dogs were made by puncturing the femoral artery with an 18 gauge needle connected directly to a mercury manometer by pressure tubing. Such determinations were made weekly or oftener.

A number of the animals which became hypertensive were treated with kidney extracts designed to lower blood pressure. The extracts were prepared by modifications of the methods published by Page, Helmer, Kohlstaedt, Fouts, Kempf and Corcoran. These extracts were sterile by bacteriologic test and were administered orally, intramuscularly, or intraperitoneally, and in a few instances intravenously. The dosage varied according to the response elicited. An evaluation of the ability of these extracts to reduce the blood pressure will be presented separately. Evidence will be presented in this paper to show that treatment with these extracts did not cause periarteritis nodosa.

RESULTS

The lesions were similar in rats and dogs and consisted of varying degrees of fibrinoid necrosis and inflammatory exudate in the walls of small and medium-sized arteries, particularly those of the mesentery, hilar regions of abdominal viscera, and in the epicardium of the right

ventricle. Acute, subacute and chronic stages were seen. The early phase consisted of fibrinoid necrosis of the media and adventitia with perivascular edema and the appearance of a few large cells resembling macrophages or histiocytes, which frequently contained many blue granules in the cytoplasm. The lesions spread to involve all three coats of the vessel walls (Fig. 1), producing a necrotizing panarteritis with pleomorphic inflammatory cellular exudation in which eosinophils were prominent. In more chronic cases, extensive granulomatous nodules were found in and around the vessel walls (Figs. 2 and 4). Frequently there was thrombosis of the lumina with varying degrees of vascular occlusion and aneurysm formation, which produced gross nodularity and angulation of vessels (Fig. 3). The mesenteric arteries were often enlarged to many times their normal caliber.

The process was largely confined to the small arteries; the arterioles only rarely were affected and when involved the lesions were not prominent. In a few cases with long-standing hypertension and extensive renal destruction, such as infarction, there was found the type of arteriolar necrosis described by Goldblatt and Kahn. Such lesions can be differentiated from those of periarteritis nodosa by the amount and type of inflammatory cellular exudation, the size of vessels involved and, to a lesser extent, by the distribution of the lesions. In arteriolar necrosis inflammatory reaction is rare, but when it occurs the cells are predominately neutrophils. In periarteritis nodosa inflammatory reaction is a prominent part even of early lesions, and the reaction is pleomorphic with neutrophils playing a minor rôle. In the abdominal viscera, arteriolar necrosis is most commonly seen in the nutrient arterioles within organs, while periarteritis nodosa is best seen in the smaller arteries in the hilum of an organ. In fact it is often limited to this site.

In the majority of the animals with periarteritis nodosa the lesions were widely distributed. Microscopic evidence of the disease was found in every organ except the lung. In a few cases of limited distribution the coronary and hepatic arteries were the vessels most frequently involved. For some unknown reason the arteries in the heart which most frequently presented lesions were those in the epicardium of the right ventricle about halfway between the apex and the atrioventricular junction. The size and histologic structure of vessels may be an important predisposing factor in the localization of the lesions.

Findings in Rats

In order to correlate various experimental factors with the occurrence of periarteritis nodosa, the 100 rats studied were divided into the following groups (the numbers of animals are noted):

A. Rats which were not treated with renal extracts and were not operated upon (28).

B. Rats which were treated with renal extract but were not operated upon (10).

C. Rats in which hypertension was induced by wrapping the kidneys with silk, but which received no renal extract (26).

D. Rats in which hypertension was induced by wrapping the kidneys with silk, but which subsequently received renal extract (36).

Group A served as controls for the other groups in regard to sex, age, strain, species, diet and environment.

Table II gives the number of cases of periarteritis nodosa found in

TABLE II
*Occurrence of Periarteritis Nodosa in Animals Subjected to
Various Controlled Procedures*

	Number of animals	Periarteritis nodosa	
		Present	Absent
Group A. No operation, no extract	28	0	28
Group B. No operation, extract treated	10	0	10
Total	38	0	38
Group C. Silk-perinephritis operation, no extract	26	6	20
Group D. Silk-perinephritis operation, extract treated	36	20	16
Total	62	26	36

each of the four groups of rats. Of the 38 which were not operated upon, none showed evidence of the disease either grossly or microscopically, while 26, or about 42 per cent of the animals which were operated upon, subsequently developed periarteritis nodosa. The odds against this association occurring by chance are greater than 16,000 to 1.*

Of the 62 rats with perinephritis induced by silk, 27 were males and 35 were females. The lesions of periarteritis nodosa were found in 14, or 52 per cent, of the males and in 12, or 34 per cent, of the females. This difference is too small to be considered significant with this number of animals.

In Table II the greater proportion of animals with periarteritis among those treated with extracts after operation is explained by the fact that extracts were given to the animals with the higher blood

* Computed according to the formula for a four-fold table as described by Raymond Pearl (Introduction to Medical Biometry and Statistics, W. B. Saunders Co., Philadelphia, 1930, ed. 2, p. 317).

pressures, and, as will be pointed out later in this report, animals with periarteritis tended to have higher blood pressures than the ones without it.

Since not all of the animals with silk-induced perinephritis developed periarteritis nodosa, the possible etiologic effect of the extracts was considered. Ten rats not operated upon received the extracts and none developed periarteritis nodosa. Thirty-six rats operated upon were subsequently given extracts. In 16, or about 45 per cent, periarteritis nodosa did not develop. Therefore, the extracts, either alone or in combination with the operation, failed to produce periarteritis nodosa in 26 animals. On the other hand, 6 rats which were operated upon but received no extracts developed periarteritis nodosa. It was concluded, therefore, that the treatment with extracts did not cause periarteritis in these rats. The possible effects of the extracts upon blood pressure will be discussed in a subsequent report.

Many of the rats of this series, both with and without periarteritis nodosa, presented extensive infectious processes, particularly suppurative lesions within the perinephric membrane. In those animals which presented periarteritis there was usually binding together of abdominal viscera by chronic granulomatous inflammation in which pockets of caseous necrosis and suppuration were found.

In the animals which did not present periarteritis nodosa the reaction around the silk was usually limited to a thin layer adjacent to the renal capsule, with very little or no involvement of the surrounding organs and tissues. Pockets of necrosis and infection were frequently not found. In some animals the reaction was so slight that the perinephric membrane was semitransparent. Sections of silk-wrapped kidneys were difficult to cut on the microtome; therefore it was considered impractical to make numerous microscopic sections of all kidneys to determine accurately the incidence of perinephric infectious processes.

Infections elsewhere in the body, such as lobular pneumonia, occurred occasionally in each group and were considered to be of no etiologic significance.

A distinct difference between the two groups of animals was disclosed by the blood pressure studies shown in Table III. In order to rule out the effect of possible errors in blood pressure readings, the mean pressures of the two groups were compared. In Table III the differences in the mean blood pressures between the rats with and without periarteritis are indicated. Statistical analysis permits the conclusion that the mean pressure of the periarteritic animals each month during

the period of observation was significantly higher than that of the non-periarteritic animals.*

The range of normal pressures was determined from 707 readings on 83 rats before operation or extract treatment. Ninety-nine per cent of the readings were between 100 and 139 mm. of mercury, the average being 122 mm.

TABLE III
Mean Blood Pressures of Rats Each Month after Last Operation

Interval after last operation		With periarteritis nodosa (A)	Without periarteritis nodosa (B)	Significance of differences $\frac{\text{Mean}_A - \text{Mean}_B}{\sqrt{(P. E._A)^2 + (P. E._B)^2}}$
1st month	Mean pressure and P. E. Number of pressures Number of animals	178.7 \pm 0.8 224 22	167.8 \pm 0.4 345 33	12.2
2nd month	Mean pressure and P. E. Number of pressures Number of animals	176.6 \pm 0.6 409 24	165.0 \pm 0.4 422 32	16.1
3rd month	Mean pressure and P. E. Number of pressures Number of animals	175.0 \pm 0.6 326 22	165.3 \pm 0.5 195 26	12.4
4th month	Mean pressure and P. E. Number of pressures Number of animals	173.4 \pm 0.7 164 15	166.9 \pm 0.7 143 16	6.6
5th month	Mean pressure and P. E. Number of pressures Number of animals	176.1 \pm 1.1 100 6	168.9 \pm 0.9 95 10	5.1
6th month	Mean pressure and P. E. Number of pressures Number of animals	189.1 \pm 1.3 78 5	168.0 \pm 0.8 69 6	13.8

Findings in Dogs

Eight dogs were operated upon. One kidney was wrapped with silk and the other kidney removed. Of these animals four developed periarteritis and only one of these received renal extract. The other four did not develop periarteritis nodosa.

As shown in Table IV, the blood pressures of dogs with periarteritis were decidedly higher than of those without this condition.

In three of the dogs with periarteritis there were suppurative foci in the perinephric membrane and beginning abscess formation in the renal substance.

In the fourth animal in which periarteritis nodosa was limited to the coronary arteries, no evidence of infection was found in the sections studied. This animal died suddenly 3 weeks after operation, having

* A difference which is three or more times its probable error is considered significant (Pearl, *loc. cit.*).

developed hypertension (215 mm. Hg) 1 week after operation. The cause of death was extensive myocardial necrosis and hemorrhage.

The four dogs which did not develop periarteritis had mild hypertension with no evidence of suppuration in the kidney or perinephric membrane. Two of the four had slight arteriolosclerosis in some of the viscera.

TABLE IV
Monthly Average Blood Pressures of Dogs
(Mm. of Mercury)

Interval after last operation	Mean pressure, probable error and number of readings							
	Dogs without periarteritis nodosa				Dogs with periarteritis nodosa			
	No. 255	No. 360	No. 392	No. 398	No. 314	No. 348	No. 358	No. 367
1st month	155 \pm 3 (8)	160 (2)	160 (1)	145 \pm 3 (6)	151 \pm 8 (10)	210 \pm 3 (3)	207 \pm 13 (3)	210 (2)
2nd month	145 \pm 3 (7)	168 (2)	170 (2)	145 (2)	199 \pm 4 (6)		248 \pm 4 (6)	275 \pm 2 (4)
3rd month	180 \pm 8 (3)	140 (2)		165 (1)			238 \pm 3 (17)	
4th month	185 (1)		205 (1)				228 \pm 5 (12)	
5th month			285* (1)					
6th month	160 (1)							
7th month	155 (1)	125 (1)						
8th month	140 (1)	135 \pm 5 (4)						
9th month	173 \pm 6 (3)	150 \pm 1 (11)						
10th month	163 \pm 2 (11)	148 \pm 3 (6)						
11th month	172 \pm 2 (10)	150 (1)						

* Died on the following day.

Periarteritis nodosa has never been encountered in the large group of dogs which have lived in the same laboratory as the above animals and which have been studied for other purposes.

COMMENT

In reviewing previous reports concerning the occurrence of periarteritis nodosa in animals it has been difficult to attribute the condition to any one factor.

The occurrence of this condition in epidemic form in the herd of axis deer cited in Table I suggests an infectious agent. However, the majority of investigators seem to think that periarteritis nodosa is not a specific disease but represents a reaction (possibly allergic) of the arterial system to a variety of infections and toxemias. Rich and Gregory have reported the occurrence of this vascular lesion in human

patients who have manifested hypersensitive reactions to serums or to a sulfonamide. They also described typical lesions in rabbits in which hypersensitivity had been induced by the administration of horse serum. Most of their animals also had acute diffuse glomerulonephritis. They described no controls or blood pressure studies.

Wilson and Byrom have noted periarteritis nodosa in certain rats made hypertensive by clamping the renal artery, and believe that the factor determining the lesion is the sudden strain imposed on the vessel wall by marked vasoconstriction and the resultant sudden rise in blood pressure. These authors did not investigate the possible relation between periarteritis and the presence of infection in their animals. Cromartie's rats, which developed periarteritis, were all hypertensive and most of them presented infection around the kidneys. Since some human patients with periarteritis nodosa apparently have not had hypertension, it seems that other factors may play a rôle in the genesis of this condition in man.

Since blood pressure levels of the two groups of hypertensive rats of the present series were essentially the same before operation and were within normal limits, it would be interesting to know how soon a significant difference began to appear. Table III shows that the rise in blood pressure following the production of perinephritis by silk had reached a fairly constant level by the end of the first month after operation. Also, this blood pressure level was decidedly higher in rats which developed periarteritis nodosa.

The question arises as to which developed first, the higher blood pressure or the periarteritis. Data are not available to answer this question since the blood pressure of these animals was not measured for 2 weeks following the second stage of the operation. Also, the possible rôle played by hypersensitivity has not been determined. These problems are now being investigated in additional series of animals.

SUMMARY

1. Periarteritis nodosa was found at autopsy in 26 of 62 rats and 4 of 8 dogs which had been made hypertensive by wrapping their kidneys with silk. No evidence of these lesions was found in groups of control animals.

2. In animals presenting periarteritis nodosa at autopsy, the monthly mean blood pressure levels had been higher than in animals in which no periarteritis nodosa was found. This higher level had been manifested within 1 month after the production of perinephritis and had been maintained throughout the 6 months of observation.

3. Suppurative lesions were common in the experimentally-produced perinephric membranes.

4. A review of the literature revealed no report of the occurrence of periarteritis nodosa in animals in which the kidneys and the blood pressure were proved to be normal.

5. In the present series of hypertensive animals the two observed differences between those which had and those which did not have periarteritis nodosa were, in the former: (1) higher mean blood pressure levels, and (2) more frequent and more extensive suppurative lesions around the kidneys.

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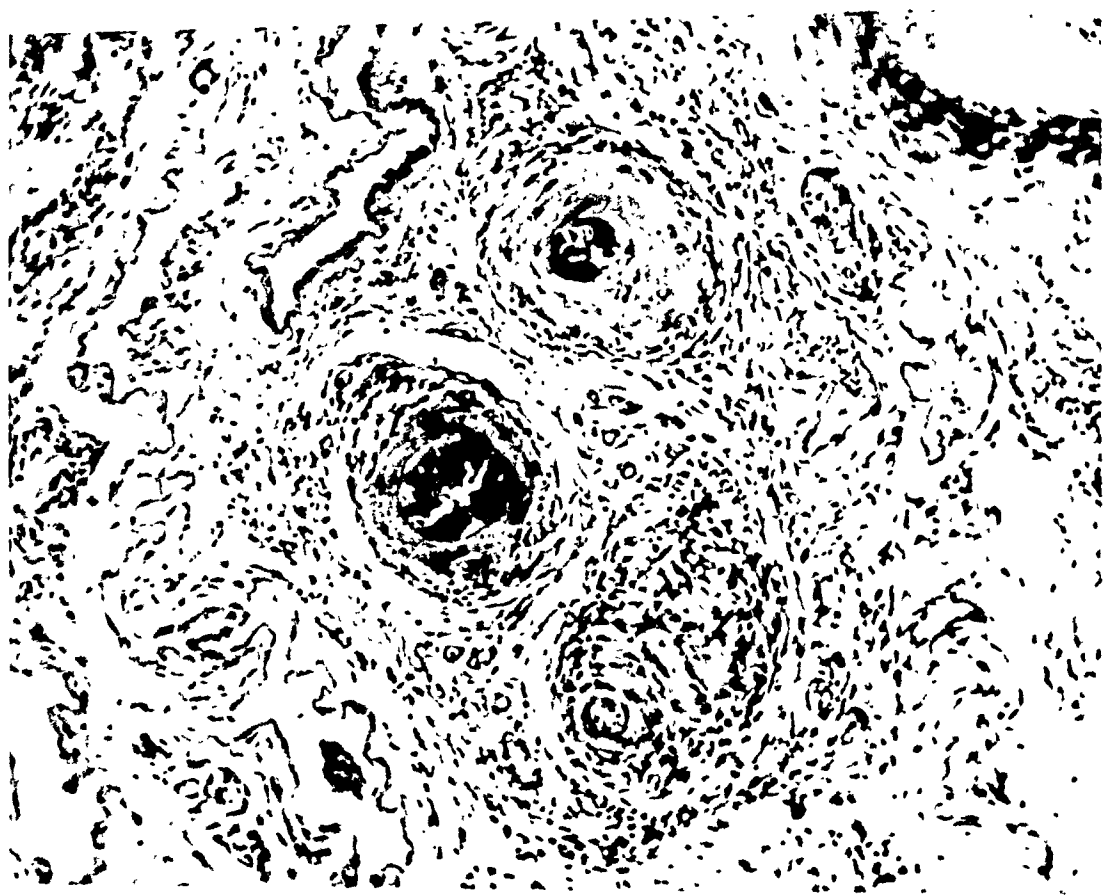
DESCRIPTION OF PLATES

PLATE 139

FIG. 1. Renal pelvis of a rat showing necrotizing periarteritis nodosa with beginning granulomatous changes. $\times 149$.

FIG. 2. Mesentery of a rat showing marked granulomatous changes of periarteritis nodosa. $\times 78$.

1



2



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PLATE 140

FIG. 3. Loop of the small intestine of a rat showing typical lesions in the mesenteric arteries.

FIG. 4. Heart of a rat showing periarteritis nodosa in wall of right ventricle. $\times 140$.



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REACTIONS OF THE BLOOD AND ORGANS OF DOGS AFTER INTRA- VENOUS INJECTIONS OF SOLUTIONS OF METHYL CELLULOSES OF GRADED MOLECULAR WEIGHTS *

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The intravenous introduction of macromolecular substances of varying molecular weights, sizes and shapes (plasma, plasma albumin, plasma globulin, hemoglobin, gelatin, isinglass, polyvinyl alcohol, methyl cellulose, gum arabic, pectin,¹⁻⁹ vinyl pyrrolidone polymer¹⁰), or of colloidal material of different particle sizes (Evans blue, Congo red, inulin, metallic colloids) is a procedure used for therapeutic purposes in shock, hemorrhage and septic infections as well as for diagnostic purposes in the determination of total plasma volume, amyloidosis and renal function. Disturbances of the macromolecular and colloidal status of the proteins, polysaccharides and lipids of the blood are found in immune reactions, myelomatosis, glycogen-storage disease, nephrosis, and diseases with lipemic reactions.

Despite the obvious frequency of abnormal fluctuations in the macromolecular, colloidal equilibrium of the blood, no systematic investigations exist concerning the rôle which the size of the aggregates eliciting such reactions plays in the development and the type of the pathological manifestations produced in the blood and organs. The present investigations were conducted in an attempt to fill this gap by using a series of methyl celluloses which are identical in chemical structure, but differ in the relative length of the dextrose chain and thus in molecular size.

EXPERIMENTAL PROCEDURE

Inasmuch as detailed information on the physicochemical properties of methyl cellulose has been recorded in previous publications (Hueper,⁴ Hueper and Ichniowski,⁹ Hueper, Martin and Thompson¹¹), it may suffice here to point out that methyl cellulose is the methyl ether of cellulose. As a hydrophilic colloid, it forms a viscous solution, from which it can be precipitated by the addition of various salts and which forms a firm, white coagulum upon heating above 65° C., reversible on cooling. It is digested by pancreatin at 40° C. with the development of reducing sugars.¹² When introduced into the blood, it forms an emulsion with the blood plasma. Table I presents the relations which exist as to grade of viscosity, molecular weight and degree of polymeri-

* Received for publication, August 30, 1943.

zation between the seven types of methyl cellulose used in this and preceding studies.

The data on the molecular weights, the degree of polymerization and the grade of viscosity for the 2 per cent solution were supplied by Dr. R. M. Upright, The Dow Chemical Company, from which the various methyl celluloses were obtained. The viscosity of the 0.25 per cent solution was determined with the Hess' viscosimeter and compared with water at 18.5° C.

The present studies were concerned mainly with six members of the series of methyl celluloses, since methyl cellulose of 400 cps. (centipoises) was employed in previous investigations (injected as a 2 per cent solution in amounts of from 25 to 130 cc. into 7 dogs). The data

TABLE I
Physicochemical Properties of Methyl Celluloses

Viscosity grade		Average molecular weight	Polymerization degree
2% sol. cps.*	0.25% sol. H ₂ O		
15	1.45	32,200	169
25	1.55	36,400	191
50	1.85	53,400	281
100	2.05	60,500	318
400	2.73	77,700	409
1500	3.95	118,200	622
4000	6.00	143,600	756

* Centipoises.

obtained on those occasions, therefore, will be mentioned only briefly for comparative purposes. The solutions of the various methyl celluloses were prepared in 1 per cent sodium chloride solution and had a viscosity of approximately 16 or 8 times that of normal plasma (methyl cellulose, 15 cps., 2.8 per cent; m.c., 25 cps., 2.4 per cent; m.c., 50 cps., 2 per cent; m.c., 100 cps., 1.8 per cent; m.c., 1500 cps., 1 per cent; m.c., 4000 cps., 0.7 per cent). While methyl celluloses of 1500 cps. and 4000 cps. gave a water-clear solution when dissolved at icebox temperature, the solutions of the other methyl celluloses were more or less turbid and had to be filtered through filter paper and Hyflo Supercel* for the removal of coarser floccules. They remained slightly turbid even after these procedures.

For the study of the more immediate hematic reactions, 40 cc. of these solutions were injected intravenously into dogs. There were 2 or 3 dogs in each group. The observation time of these reactions was 24 hours. The prolonged experiment started immediately thereafter

* Hyflo Supercel is a preparation of purified diatomaceous earth, obtained from the Dicalite Co., 120 Wall Street, New York, N.Y.

and consisted in the intravenous injection of methyl cellulose solution 5 days per week in rising amounts. The daily dose was 40 cc. during the first week, and was increased by 10 cc. each week until 130 cc. was reached for those dogs which survived longest. The average weight of the 18 dogs used in these and previous experiments was 9.3 kg. and the weight range was between 7 and 12 kg. The observation time varied for the different dogs from 1 week to 6 months. Examinations of the blood (hemoglobin, number of erythrocytes and leukocytes, coagulation time, sedimentation rate, volume of packed cells, plasma viscosity) were made at intervals of 2 weeks. Autopsies were performed on all dogs.

A. HEMATIC REACTIONS AFTER THE INTRAVENOUS INJECTION OF A SINGLE DOSE OF METHYL CELLULOSE SOLUTION

Examinations of the blood were made 5, 15, 30, 60, 120, 240 minutes and 24 hours after the injection, following the standard determinations.

a. Methyl Cellulose, 15 cps. (Two Dogs)

Erythrocytes. During the first 120 minutes there occurred in both dogs moderate to severe downward fluctuations of the number of erythrocytes, amounting to from 1.5 to 3 million cells. Thereafter the number of erythrocytes became stationary at a level slightly to moderately below the original one.

Hemoglobin and Volume of Packed Cells. Variations in hemoglobin and volume of packed cells ran parallel to those of the erythrocytes.

Leukocytes. There was a moderate to severe leukopenia 5 to 15 minutes after the injection, followed by return to approximately the original level within 2 hours.

Clotting Time. There were no significant deviations in clotting time.

Sedimentation Rate. There occurred a marked acceleration of the erythrocytic sedimentation rate before 4 hours after the injection. This was followed by a considerable decrease at the 24 hour test.

Plasma Viscosity. The plasma viscosity was moderately increased (0.5 to 0.1) beyond the normal range immediately after the injection, and returned to normal at the 4 hour test.

b. Methyl Cellulose, 25 cps. (Two Dogs)

The hematic reactions followed closely in pattern those seen in the animals of the previous group, with the exception of the sedimentation rate which was already markedly increased at the 5 minute test, and remained high to the end of the observation period (24 hours).

c. Methyl Cellulose, 50 cps. (One Dog)

Erythrocytes. Following an increase by 1.35 million at the 5 minute level, the erythrocytes remained relatively stationary around the original level during the 24 hour observation period.

Hemoglobin and Packed Cell Volume. The hemoglobin values, as well as the figures obtained from hematocrit determinations, remained below the original level throughout the 24 hours, exhibiting a tendency to drop progressively.

Leukocytes. Transitory leukopenia reached its lowest level at the 15 minute test. The leukopenic crisis had completely disappeared at the 4 hour test.

Clotting Time. No significant changes in clotting time were found.

Sedimentation Rate. Sedimentation was definitely hastened at the 5 minute test, and was moderately accentuated during the 24 hour period.

Plasma Viscosity. There was a marked increase in plasma viscosity directly after injection (1.25). This reaction subsided somewhat during the first 4 hours, at the end of which the increase in viscosity had dropped to 0.35; but this was followed by a renewed increase after 24 hours by 1.6 points (to 3.75) above the original level (2.15).

d. Methyl Cellulose, 100 cps. (Three Dogs)

Erythrocytes. With the exception of 1 dog which showed an initial rise in the number of the erythrocytes at the 5 minute test, amounting to 1.15 million, the erythrocytes remained relatively stationary during the first 2 hours and decreased moderately in 2 dogs from then on.

Hemoglobin and Volume of Packed Cells. There was a definite tendency to reduced values for both hemoglobin and volume of packed cells with the progress of the test.

Clotting Time. No deviations from the normal range of clotting time were noted.

Sedimentation Rate. Sedimentation of erythrocytes was definitely accelerated at the 5 minute test, and was accentuated during the further course of the experiment. The sedimentation rate thus remained persistently high during the 24 hour observation period.

Plasma Viscosity. The plasma viscosity was moderately increased immediately after the injection (0.65 to 1.0 point) and remained elevated during the entire period.

e. Methyl Cellulose, 400 cps. (Three Dogs)

Erythrocytes. There was a mild reduction in erythrocytes during the first 4 hours, followed by a return to the original level at the 24 hour test.

Hemoglobin and Volume of Packed Cells. The hemoglobin values dropped from the 5 minute test on, and remained reduced during the entire 24 hour period. Hematocrit values followed a similar trend.

Leukocytes. Transitory leukopenia lasted from 2 to 4 hours, and was followed by leukocytosis at the 24 hour test.

Clotting Time. There was a lengthening of the clotting time appearing 15 minutes to 2 hours after the injection and persisting in 2 dogs at the 24 hour test.

Sedimentation Rate. Acceleration of erythrocytic sedimentation was marked at the 5 minute test and persisted for more than 24 hours.

Plasma Viscosity. Plasma viscosity was markedly increased immediately after injection and then showed a moderate drop, but remained considerably above the original level during the entire 24 hours.

f. Methyl Cellulose, 1500 cps. (Three Dogs)

Erythrocytes. There was no consistent or appreciable variation in the number of red cells during the first 15 minutes. All dogs showed during some time thereafter a moderate reduction in erythrocytes.

Hemoglobin and Volume of Packed Cells. Fluctuations in hemoglobin and volume of packed cells paralleled in general those in the number of red cells.

Leukocytes. Transitory leukopenia lasted for 4 hours or more.

Clotting Time. There was a minor to moderate increase in the clotting time during the first hour with a return to normal values thereafter.

Sedimentation Rate. The hastening of the erythrocytic sedimentation was pronounced at the 5 minute test and remained high or even increased during the remainder of the observation period.

Plasma Viscosity. Increase in the plasmatic viscosity was mild and did not persist for longer than 30 minutes.

g. Methyl Cellulose, 4000 cps. (Three Dogs)

Erythrocytes. Following a moderate brief reduction in erythrocytes some time during the first 45 minutes, the number of red cells returned to approximately the original level for the remainder of the 24 hour period.

Hemoglobin and Volume of Packed Cells. The hemoglobin was comparatively decreased, particularly during the latter part of the experimental period. The hematocrit values showed a similar movement.

Leukocytes. Transitory leukopenia extended beyond the 4 hour test. A moderate to marked leukocytosis was found in 2 dogs at the 24 hour examination.

Clotting Time. No significant deviations in clotting time were observed.

Sedimentation Rate. The increase in erythrocytic sedimentation was moderate during the first 45 minutes and became considerable and persistent thereafter.

Plasma Viscosity. There was a mild increase in the plasmatic viscosity not surpassing the normal range, which persisted throughout the experimental period.

The hematic reactions observed in dogs following the intravenous introduction of 40 cc. of solutions of the seven types of methyl cellulose prepared in normal saline solution and having the same viscosity (8 times that of plasma) revealed the following pattern and discrepancies. The number of erythrocytes exhibited in all instances a tendency toward a mild to moderate decrease, particularly toward the latter part of the observation period. This movement was displayed more consistently and considerably by the amount of hemoglobin and the volume of packed cells, especially with the methyl celluloses of higher molecular weight. A leukopenic reaction was noted with all types of methyl cellulose, but the leukopenic crisis was least persistent with the methyl celluloses of low molecular weight, while lasting for more than 4 hours with those of higher molecular weights, in connection with which the reaction was not infrequently followed by a leukocytosis at the 24 hour test.

Abnormalities in clotting time were found only with methyl celluloses of 400 and 1500 cps. and especially with the former. The sedimentation rate was increased with methyl celluloses of all types. However, this acceleration showed a delayed appearance with the two low molecular methyl celluloses, compared with the immediate hastening found with the other types. It was noted, moreover, that this response was of lesser duration with the low molecular products, whereas it was of higher severity and greater duration with the higher molecular substances. The plasma viscosity was increased in all instances immediately after the injection. This increase was of relatively short duration and low intensity with the two low molecular methyl celluloses. It was of higher intensity and long duration with the medium molecular substances and of low intensity and long duration with those of high molecular weights, while no pathological increase resulted from the injection of the methyl cellulose of highest molecular weight.

B. HEMATIC REACTIONS AFTER THE INTRAVENOUS INJECTION OF REPEATED DOSES OF METHYL CELLULOSE SOLUTION

Blood tests were made at intervals of 2 weeks, unless severe changes necessitated a more frequent control of the status of the blood.

a. Methyl Cellulose, 15 cps. (Two Dogs)

One dog received within 2 weeks a total of 570 cc. of methyl cellulose solution, while the second dog was injected within 18 days with 670 cc. Both dogs died.

Erythrocytes. There was a moderate decrease in the number of red cells, ranging from 1.1 to 1.8 millions below the original value.

Hemoglobin and Volume of Packed Cells. The decrease in hemoglobin and in volume of packed cells comparatively surpassed that of the erythrocytes to a minor degree.

Leukocytes. There were no pathological fluctuations in the number of leukocytes.

Clotting Time. No abnormal deviations in clotting were noted.

Sedimentation Rate. There was a marked increase in the sedimentation rate.

Plasma Viscosity. Toward the end of the experimental period the plasma viscosity was elevated by 50 to 100 per cent above its normal level.

b. Methyl Cellulose, 25 cps. (Two Dogs)

One dog received a total of 1580 cc. of methyl cellulose solution within 52 days, whereas the second dog was injected with 130 cc. within 11 days. Both dogs died.

Erythrocytes. The red cells dropped by more than 66 per cent in the dog surviving for 52 days (from 6 million to 1.65 million).

Hemoglobin and Volume of Packed Cells. The reduction in the amount of hemoglobin was approximately equal to that of the erythrocytes, while the decrease in the volume of the packed cells even surpassed the drop of the erythrocytes.

Leukocytes. There was a temporary moderate leukocytosis followed during the latter part of the experiment by a return to normal values.

Clotting Time. No abnormalities in clotting time were noted.

Sedimentation Rate. The sedimentation of the erythrocytes was highly and increasingly accelerated.

Plasma Viscosity. The plasma viscosity rose to a peak of 4.9, 4 weeks after the start and then gradually dropped back to 3.25, rising again toward the end to 4.5.

c. Methyl Cellulose, 50 cps. (Four Dogs)

One dog was injected with 290 cc. of methyl cellulose solution within 10 days, a second with 370 cc. within 12 days, a third with 1320 cc. within 32 days, and a fourth with 2010 cc. within 75 days. All dogs died.

Erythrocytes. In all dogs there was a progressive, and ultimately considerable, decrease in the number of erythrocytes. In the dog sur-

viving 75 days the drop was from 6.21 million to 1.42 million, following a temporary partial recovery during a period in which the injections were discontinued.

Hemoglobin and Volume of Packed Cells. The reduction in hemoglobin was considerable and progressive and reached in the aforementioned dog a level of less than 5 gm. per 100 cc. of blood. The decrease in the volume of packed cells was relatively more pronounced than the decrease of red cells in those animals having a moderate anemia, while it was comparatively less definite in the dog with the severe anemia after having passed previously through the first mentioned relation.

Leukocytes. There was a moderate leukocytosis present during the latter part of the experimental period.

Clotting Time. There were no abnormalities in clotting time.

Sedimentation Rate. There was a very marked acceleration of the sedimentation rate (75 to 79 mm., Wintrobe tube).

Plasma Viscosity. The plasma viscosity was considerably elevated, varying in 3 dogs between 4.9 and 6.0, after having undergone during the early part of the experiment a considerable increase followed during the middle part by a decrease to slightly elevated levels when the injections were discontinued and subsequently again by a marked elevation following the resumption of the treatment.

d. Methyl Cellulose, 100 cps. (Three Dogs)

One dog received 80 cc. within 7 days, a second dog was injected with 4645 cc. within 90 days, and a third dog with 5190 cc. within 97 days. All died.

Erythrocytes. After 2 weeks of treatment there developed a rapidly progressive and severe reduction in the number of red cells, causing after 2 months a drop to one-third and one-fourth, in the respective surviving animals, of the original number. When the treatment was then discontinued, there followed a rapid rise in the number of erythrocytes, which amounted to from 2 to 2.5 million within 2 to 3 weeks. There was, however, a very rapid drop in erythrocytes when the injections were again given, reaching values of 2.4 and 1.35 million, respectively, before death.

Hemoglobin and Volume of Packed Cells. The hemoglobin followed in general the fluctuations of the erythrocytes and sank ultimately below 5 gm. per 100 cc. of blood. The volume of packed cells dropped during the first half of the erythrocytic decrease, comparatively very sharply surpassing the reduction of the red cells, while during the latter part of the experiment the decrease in the volume of packed cells was relatively smaller than that of the erythrocytes.

Leukocytes. There were no significant deviations in the number of leukocytes from the normal range, except during the final days, when a moderate leukocytosis existed.

Clotting Time. No abnormalities in clotting time were noted.

Sedimentation Rate. An early and marked acceleration of erythrocytic sedimentation persisted through the treatment-free period to the end.

Plasma Viscosity. The plasmatic viscosity was increased to slightly above 6 during the major part of the experiment, except during the treatment-free period, when the viscosity dropped to values between 2.5 and 3.5.

e. Methyl Cellulose, 400 cps. (Seven Dogs)

One dog received 260 cc. of methyl cellulose solution within 6 days, a second and a third animal were injected with 1040 cc. within 12 and 13 days respectively, a fourth dog was injected with 2112 cc. within 57 days, a fifth received 2930 cc. within 66 days, a sixth 3375 cc. within 83 days, and a seventh 5720 cc. within 6 months. The first 3 dogs died, while the other 4 were killed. The seventh animal was sacrificed 2 months after the last injection, while the others were sacrificed not later than a few days after the last treatment.

Erythrocytes. There occurred a gradual decrease in the number of erythrocytes, which reached, however, severe degrees only in those animals which died, remaining within a moderate range in those which survived the prolonged treatment for many weeks and were finally sacrificed. It was noted, moreover, that during a temporary discontinuation of the treatment a relatively rapid increase in the number of red cells developed. This was especially striking in the dog which was killed 2 months after the last injection and which showed a recovery to the original erythrocytic level 1 week after cessation of treatment.

Hemoglobin and Volume of Packed Cells. The hemoglobin decreased during the early part somewhat more rapidly than the erythrocytes, but exhibited a normal relation to the cellular elements in the latter part of the experiments. The volume of packed cells underwent a similar movement.

Leukocytes. The number of white cells fluctuated within the normal range, sometimes reaching relatively low figures.

Clotting Time. The clotting time was rather consistently and considerably increased, and decreased slowly after cessation of treatment.

Sedimentation Rate. Erythrocytic sedimentation was considerably hastened during the entire time of treatment and showed a gradual return toward normal values after cessation of injections.

Plasma Viscosity. The plasma viscosity was markedly increased during the course of treatment and particularly so during the last days of those dogs which died spontaneously. In those animals it reached values up to 7.88 after relatively few injections. In dogs with more prolonged and severe treatment this value was often surpassed during the more advanced stages, reaching 9.68. The viscosity remained at a high level for weeks after the cessation of injections, showing a slow decline.

f. Methyl Cellulose, 1500 cps. (Three Dogs)

One dog received a total of 990 cc. of methyl cellulose solution within 4 weeks. A second dog was injected with 2330 cc. within 7 weeks and a third with 4590 cc. within 11 weeks. All died.

Erythrocytes. The number of erythrocytes decreased after prolonged treatment to less than one-third of the original value.

Hemoglobin and Volume of Packed Cells. The hemoglobin was considerably reduced and reached in 2 dogs values below 5 gm. per 100 cc. of blood. The decrease of hemoglobin thus surpassed that of the erythrocytes. The reduction in the volume of packed cells, on the other hand, was somewhat less in degree than that of the erythrocytes.

Leukocytes. The leukocytes were always either at a high normal level or slightly above that range.

Clotting Time. No abnormalities in clotting time were found.

Sedimentation Rate. There was a marked hastening of the erythrocytic sedimentation.

Plasma Viscosity. The plasma viscosity was only moderately increased, reaching as peak value a viscosity of 4.

g. Methyl Cellulose, 4000 cps. (Three Dogs)

One dog received 2290 cc. of methyl cellulose within 6 weeks, a second was injected with a total of 3440 cc. within 8 weeks, and a third dog with 4930 cc. within 12 weeks. All died.

The hematic changes were similar to those seen in the series injected with methyl cellulose, 1500 cps. This was particularly so in regard to the increase in plasma viscosity, which remained below 3.5. It is remarkable that the dog which received 2290 cc. of methyl cellulose developed an anemia of 850,000 erythrocytes and a leukocytosis of 100,000 cells 3 days before death. In the dog which was injected with 4930 cc. the final erythrocytic number was 1.45 million (originally 8 millions) and the final leukocytic number, 42,600 cells.

The hematic reactions noted after repeated intravenous injections of the seven types of methyl cellulose exhibited a uniform pattern in many respects, but certain important deviations in others. There was in all

instances a considerable decrease in the number of the circulating erythrocytes, in the amount of hemoglobin and in the volume of packed cells, which was especially pronounced with the higher molecular types. The reduction of the last two items usually surpassed in degree that of the erythrocytes. It was evident, moreover, from the instances in which the treatment was interrupted for some time, that this anemia-producing effect was relatively readily reversible if the further introduction of the causative agent was stopped. As a rule, the leukocytes stayed within the normal range, but sometimes were slightly to moderately increased during the final stage. This reaction was especially pronounced in the dogs injected with m.c., 4000 cps., one of which exhibited a marked hyperleukocytosis of leukemoid type. The clotting time underwent abnormal changes only in animals injected with m.c., 400 cps., in which it was considerably lengthened. The sedimentation rate was definitely accelerated in all instances and remained so for some time after discontinuation of treatment. The plasma viscosity was always increased. However, this increase was comparatively small with the methyl celluloses of the low and the high molecular weights (m.c., 15 cps., 25 cps., 1500 cps., 4000 cps.), while it was highest with methyl cellulose of 400 cps. having a molecular weight approximating that of serum albumin. It was noted, moreover, that the elevated viscosity dropped rather rapidly to slightly increased values after discontinuation of treatment in dogs injected with methyl celluloses of 50 cps. and 100 cps., whereas it stayed considerably elevated for periods of many weeks after cessation of injections in dogs treated with methyl cellulose of 400 cps.

C. ANATOMICAL REACTIONS IN THE INTERNAL ORGANS FOLLOWING REPEATED INJECTIONS OF METHYL CELLULOSE

a. Methyl Cellulose, 15 cps. (Two Dogs)

The 2 dogs of this series received 570 and 670 cc. of methyl cellulose solution respectively, and showed at autopsy practically normal organs with the exception of a large pneumonic induration in the left upper lobe of 1 dog. The spleens were of normal size, of firm consistency and grayish pink.

The histological study of the various organs showed the following findings:

Thyroid; Aorta; Pulmonary Artery; Large Elastic Arteries; Muscular Arteries of Thyroid, Kidney and Adrenal; Pancreas; Stomach and Intestine; Bladder. Normal.

Lung. Purulent bronchitis and large bronchopneumonic foci were present in the lungs of both dogs. There were deposits of a homogene-

ous, vacuolated, light-blue-stained matter in the peribronchial tissue spaces of 1 dog.

Heart. Small bluish-colored homogeneous deposits were found in the myocardial interstices.

Liver. Pericentral fatty degeneration or necrosis of liver cells.

Adrenals. Small bluish deposits were present in the sinusoids of the adrenals of 1 dog.

Spleen. The pulp consisted of accumulations of small foam cells, many of them in a stage of disintegration. Follicles were atrophic.

Kidney. The cortical tubules were distended, cystic, and lined by flattened epithelium. Some of the glomeruli showed grape-like, distended, cystic, capillary loops containing foam cells, or, occasionally were lined by a multinucleated syncytium, which was found also in the lining of some tubules. The interstitial tissue of 1 dog contained bluish homogeneous deposits in the interstices. Renal vessels were normal.

Testes. Arrest of spermatogenesis was present in both dogs. This was associated in 1 dog with the presence of some spermatid giant cells and interstitial edema and was accompanied in the second dog by a severe atrophy of the spermatogenic epithelium, leaving only the spermatogonia and the Sertoli's cells preserved. Some of the tubules were collapsed.

Bone Marrow. There was in the sternum a loose, hyperemic, immature myeloid tissue.

b. Methyl Cellulose, 25 cps. (Two Dogs)

The two dogs of this series received a total of 350 and 1580 cc. of methyl cellulose solution respectively, and showed at autopsy, apart from emaciation, normal internal organs.

The histological examination of the organs revealed the following findings:

Brain; Hypophysis; Parathyroid. Normal.

Thyroid. The follicles contained a thin colloid or were empty. In 1 dog the epithelial lining was desquamated in some follicles. The thyroid of the second dog which received the larger dose of methyl cellulose was normal.

Lung. The lungs were highly edematous, congested and hemorrhagic in the first dog and normal in the second dog.

Heart. The heart was normal in the first dog. The walls of the sub-epicardial coronary arteries in the heart of the second dog were transformed, particularly in their intimal portion, into a thick foam-cellular tissue considerably narrowing the lumina. Similar lesions were found in the myocardial arteries and arterioles. The subendocardial myo-

cardium of the left ventricle, especially of the papillary muscles, contained large and numerous calcium incrustations of necrotic muscle cells in addition to foci of loose fibrous tissue replacing muscle tissue (Fig. 1).

Aorta. The ascending aorta of the first dog showed a granular necrosis in the thickened intima and adjacent media. In a nearby segment the outer and middle media contained large hyaline areas with an extensive nodular calcification causing a bulging of the vessel wall into the lumen. The subintimal media was edematous. In the thoracic aorta there was perivascular hyalinization around vasa vasorum in the middle media. The aorta of the second dog exhibited similar and extensive medial hyalinization and calcification in the media of the aortic bulb, which showed, moreover, a thin foam-cellular coating and small foam-cellular cushions of the intima. In the thoracic part of the aorta extensive lesions of these types were present. The vasa vasorum of the adventitia were partly obliterated by foam-cellular intimal proliferations, while large portions of the media were hyalinized.

Pulmonary Artery. There were areas of medial calcification above the valves together with some foam-cellular intimal cushions in the second dog.

Large Elastic Arteries. Some large elastic arteries of the second dog showed extensive calcification of the media in some areas and in other parts incrustation of the elastic fibrils together with cyst formation. In several segments these lesions were associated with foam-cellular proliferation of the intima (Fig. 2).

Stomach. There was a diffuse fine granular calcification in the interstitial tissue of the mucosa in the second dog.

Liver. Extreme congestion and extensive fresh coagulation necrosis of the liver cells characterized the lesions of the first dog. The Kupffer cells of the second dog were markedly increased in number and had foamy cytoplasm. The cell cords were pushed apart thereby and the hepatic cells were moderately atrophic.

Pancreas. A medium-sized artery in the normal pancreatic parenchyma of the second dog showed intimal foam-cellular cushions and medial subendothelial calcium deposits.

Spleen. The organ was normal in the first dog and showed a pulp composed of foam cells in the second dog.

Adrenals. These organs were normal in the first dog and contained foam-cellular reticulo-endothelial cells of the medulla in the second dog.

Kidney. The tubules of the cortex were distended, cystic, and lined with flattened cells in both dogs. The glomeruli were hypertrophic and showed extensive hyalinization in the first dog. In the second dog many

consisted of a few cystic structures lined by foam cells or by a multinucleated syncytium. The arterioles in the kidney of the first dog had a distinct, thick, red-stained subintimal layer, while the arteries of the second dog showed a few foam-cellular cushions of the intima undergoing degenerative changes.

Testes. The spermatogenic epithelium of the tubules was reduced in the second dog to the spermatogonia and Sertoli's cells with a few large giant cells. The arterioles revealed a hyaline subendothelial thickening.

Epididymis. The ducts were empty.

Bone Marrow. The sternum contained a dense, immature myeloid tissue.

c. Methyl Cellulose, 50 cps. (Three Dogs)

One dog was injected with 370 cc. of the methyl cellulose solution, a second with 1120 cc. and a third with 2010 cc. The lungs were edematous, hyperemic and studded with dark red, hemorrhagic foci. The spleens of the second and third dogs were enlarged, soft and grayish pink. The livers of these animals were large, and brown with a grayish tint. All other organs were grossly normal.

The histological examination of the organs gave the following findings:

Vena Cava; Stomach and Intestine; Pancreas; Mesenteric Lymph Nodes. Normal.

Brain. The choroid plexus of the third dog, which received the highest amount of methyl cellulose, consisted of a dense and bulky accumulation of foam cells lined by an intact ependyma. The brains of the other dogs were normal.

Lung. The blood vessels in the interalveolar septa and in the peribronchial tissue were frequently transformed in all 3 dogs into small multicystic structures lined by a syncytium, filled with a colorless, slightly refractive substance, and surrounded by granulation tissue containing large round cells.

Heart. The coronary arteries of the third dog had a thick, foam-cellular intima infiltrating into the media.

Aorta. There was only a minor foam-cellular intimal proliferation involving endothelium and subendothelial tissue in the bulb of the first dog, which showed in a thoracic segment an extensive hyaline and collagenous transformation of the media with marked vascularization (Fig. 3). The intimal foam-cellular cushions in the aortic bulb were more highly developed in the second and third dog, and contained in the second dog a few leukocytes (Fig. 4), while the underlying media showed scattered calcium granules. The thoracic and abdominal seg-

ments of the aortas of these 2 dogs exhibited frequent and marked intimal foam-cellular proliferations which sometimes invaded the intima and also involved the vasa vasorum. The media was often highly edematous or mucoid. A mucoid, small-vesicular zone extended between intima and media. Intimal hyalinization was found occasionally, whereas the media contained larger areas of calcification in both the inner and the hyalinized outer medial zone.

Pulmonary Artery. There was a moderate foam-cellular thickening of the intima of the pulmonary artery near the hilum in the second dog.

Large Elastic Arteries. The large elastic arteries were normal in the first dog, but contained foam-cellular intimal thickenings in the other 2 dogs. The nuclei of these foam cells had sometimes grotesque spider-like chromatin.

Liver. Pericentral congestion and necrosis of liver cells were present in the first dog, while there was increase in size and a foam-cellular transformation of the Kupffer cells and of the interstitial tissue histiocytes in the other 2 dogs. The liver cells were moderately atrophic.

Adrenals. Foam-cellular reticulum cells were found in the medulla of the adrenal of the third dog.

Spleen. The splenic pulp consisted in all 3 animals of large masses of foam cells, none of them invading the lumina of the larger vessels.

Kidney. The cortical tubules were distended and lined by flattened cells. The glomeruli of the second and third dogs showed grape-like cysts. A medium-sized extrarenal artery contained a mushroom-like, hyaline, intimal thickening with underlying thickened but fragmented internal elastic membrane.

Uterus. The uterine arteries of the third dog exhibited a marked foam-cellular proliferation of the intima, often obliterating the lumina (Fig. 5).

Bone Marrow. The sternum contained a hyperemic, immature myeloid tissue.

d. Methyl Cellulose, 100 cps. (Three Dogs)

One dog was injected with 280 cc. of methyl cellulose solution, a second dog received 4645 cc., and a third, 5190 cc. The autopsy showed the lungs to be congested and edematous and containing scattered dark red hemorrhagic areas. The livers in the second and third dogs were enlarged. The spleens of these two animals were about two or three times normal size and each weighed 120 gm. They were grayish red and soft. The renal cortices of these 2 dogs contained numerous wedge-shaped white areas. All other organs were grossly normal.

The histological examination of the organs gave the following findings:

Brain; Thyroid; Large Elastic Arteries; Stomach and Intestine; Pancreas; Lymph Nodes; Bladder. Normal.

Hypophysis. The loose and increased stroma of the predominantly eosinophilic parenchyma contained foam cells in the second and third dogs (Fig. 6).

Parathyroid. Interstitial tissue of the parathyroid glands was increased and contained some foam cells in the third dog.

Lungs. The lungs of the first dog were congested and edematous and showed scattered hemorrhagic areas. The lungs of the second and third dogs contained distended cystic vascular lumina in the peribronchial and interstitial septa, surrounded by multinucleated syncytia and large round cells, fibroblasts and foam cells.

Heart. With the exception of some round cell infiltrations in the myocardium of the second dog, the hearts were normal.

Aorta. The intima of the ascending aorta of the first dog was intact, while the media showed a considerable mucoid imbibition causing the production of small cavities filled with mucoid matter, and a wide separation of the muscle bundles. The media of the thoracic part contained several large hyaline areas. The intima of the aortas of the second and third dogs was transformed into a multilayered foam-cellular coat in which cushion-like foam-cellular thickenings were embedded, which in places extended into the media. These changes were most marked in the bulb. There was an extensive subendothelial calcification in some areas.

Pulmonary Artery. Similar, but not as extensive, intimal and medial lesions, especially also muscular calcifications, were present in the post-valvular portion of the second and third dogs, while the media of the first dog revealed increase of the mucoid content (Fig. 7).

Abdominal Muscular Artery. There was a large area of medial necrosis present, associated with calcification of the elastic fibrils (Fig. 8).

Liver. The liver cells of the first dog were atrophic and the organ was congested. In the second and third dog there was also an atrophy of the liver cells. The cords were pushed far apart by proliferated, foam-cellular Kupffer cells.

Spleen. The splenic pulp of the first dog was hyperemic and cellular, whereas those of the second and third dogs were filled with foam cells which were disintegrating in places.

Adrenals. The adrenals were normal in the first and second dog, but showed foam-cellular reticulo-endothelial cells in the medulla of the third dog.

Kidney. The cortical tubules were distended in all 3 dogs. The glomeruli of the first dog were swollen and rich in nuclei, while the arterioles showed focal hyalinization of the media. The cortices of the second and third contained foci of large mononuclear cells intermingled with a foam-cellular matrix. The glomeruli were transformed into grape-like, cystic formations lined with foam cells or multinucleated syncytia.

Testes. In the second and third dogs there were a few spermatid giant cells in the testicular tubular lumina, which were lined by a generally normal epithelium.

Bone Marrow. The sternum contained a loose myeloid tissue.

c. Methyl Cellulose, 400 cps. (Seven Dogs)

One dog was injected with 260 cc. of methyl cellulose solution, a second and third with 1040 cc., a fourth with 2112 cc., a fifth with 2930 cc., a sixth with 3375 cc., and a seventh with 5720 cc.

The spleens were considerably enlarged in all dogs, including the first one. The organ was grayish pink, soft, and had in some instances an almost liquid, dirty yellow pulp. The weights varied from 230 to 400 gm. The livers were also enlarged, brown-red to brown-gray and displayed a yellowish white network. One liver weighed 1015 gm., while the others were around 500 to 700 gm. The kidneys were large with some retractions in a sometimes gelatinous cortex. The lungs were congested.

Histological examination gave the following findings:

Thyroid and Parathyroid; Stomach; Pancreas; Bladder. Normal.

Brain. The choroid plexuses of dogs 5 and 7 consisted of accumulations of foam cells. Numerous small perivascular glial foci were present in the brain of dog 3, while numerous hemorrhages were found in dog 1.

Hypophysis. Large masses of foam cells separated strands of acidophilic cells in the anterior lobe in dog 7.

Lung. Apart from congestion and the presence of numerous, moderately large round cells with an empty cytoplasm in the interalveolar septa, no pathological lesions were seen in the lungs of dogs 1 to 6. Foam-cellular masses filled the capillaries of dog 7 and formed nodules in the interstitial tissue.

Heart. The myocardium was normal in dogs 1 to 6. There were perivascular foam-cellular foci around the myocardial arteries and arterioles in dog 7. Hyaline thickenings of the media of the myocardial arterioles were present in dogs 3, 6 and 7, associated with foam-cellular intimal proliferations in dogs 6 and 7. Foam cells lined the surface of the aortic valves and the endocardium of the left ventricle in dog 7.

Aorta. The aorta was normal in dogs 1 and 2. The intima of the aortas of the other 5 dogs showed an often multilayered foam-cellular coating and cushion-like thickenings which were most strikingly developed in the aortic bulb and decreased toward the abdominal portion. The media underneath these lesions showed hyaline degeneration sometimes associated with scattered small or large nodules of calcification. Other portions exhibited an increase of the intercellular mucoid matter, which occasionally contained some foam cells.

Pulmonary Artery. The intima consisted of 2 or 3 layers of foam cells covering and invading a hyalinized media, in dogs 4 and 5.

Large Elastic Arteries. Intima showed a foam-cellular coating and small cushions in dogs 4, 5, 6 and 7, while a thickened hyaline intimal cushion was noted in one artery of dog 3.

Muscular Arteries. The intima exhibited occasionally small foam-cellular groups in dog 5.

Vena Cava. The intima consisted of foam cells in dog 6.

Intestine. The mucosa contained foam cells in the interstitial tissue in dogs 6 and 7.

Liver. While the liver of dog 1 showed only scattered foam-cellular granulomatous formations and those of dogs 2 and 3 were merely congested, the livers of dogs 4, 5, 6 and 7 revealed an extensive proliferation of Kupffer cells with transformation into foam cells. The liver cells themselves had in part a vacuolated or foam-cellular appearance. In dog 7 the periportal connective tissue participated in the foam-cellular transformation, which affected also, in part, the endothelium of the hepatic veins.

Spleen. The splenic pulps were always foam-cellular and contained clusters of large multinucleated giant cells arranged in circles. There were large areas of necrosis present. The follicles were atrophic.

Lymph Node. Foam-cellular reticulum cells were found only in dog 7.

Adrenal. Foam-cellular reticulo-endothelial cells in the medulla and glomerulosa of the adrenals were found in dogs 6 and 7. The adrenals were normal in the other dogs.

Kidney. There were a few giant-cellular and foam-cellular granulomas in the interstitial, perivascular tissue of the cortex in dogs 1, 2 and 3. A few glomeruli contained small cystic formations with foam cells. The lesions were much more widespread and severe in dogs 4 to 7, where the glomeruli had a multicystic appearance with endothelial foam cells. The tubules were distended and lined either by flattened cells or by foam cells. Foam-cellular accumulations were seen also in

the interstitial tissue. Foam-cellular proliferations of the intima of intrarenal arteries were present in dog 5 together with medial hyalinizations in the main renal artery.

Testes. Arrest of spermatogenesis existed in dog 2; marked degeneration of the spermatogenic epithelium with the appearance of numerous multinucleated giant cells occurred in dogs 3 and 4.

Uterus and Ovary: Normal in dog 6.

Bone Marrow. The sternum contained an immature myeloid tissue in dogs 1 to 6, while a few foam-cellular reticulum cells were present in an immature myeloid and fatty marrow in dog 7.

f. Methyl Cellulose, 1500 cps. (Three Dogs)

One dog was injected with 990 cc. of methyl cellulose solution, a second with 2330 cc., and a third with 4590 cc. At autopsy the lungs were found to be congested and edematous with hemorrhagic spots; the spleens were enlarged, weighing between 174 and 264 gm.; the livers were brown-red and moderately to markedly enlarged (590 to 920 gm.).

Histological examination showed the following findings:

Brain; Hypophysis; Thyroid and Parathyroid; Large Elastic Arteries; Stomach and Intestine; Pancreas; Lymph Node; Adrenals; Bladder. Normal.

Lung. Numerous distended and multicystic capillaries were found in the interstitial tissue of the lungs. The cysts were lined by a multinucleated syncytium and surrounded by foam cells and large mononuclear cells.

Heart. The myocardium was normal. There were marked foam-cellular proliferations in the intima of the epicardial and myocardial coronary branches in dog 1.

Aorta. The ascending aorta showed a foam-cellular lining of moderate extent and thickness in all 3 dogs. The underlying media was thickened by imbibition of mucoid material. In other parts of the aorta there were some cushion-like foam-cellular intimal thickenings in dogs 1 and 3. The deeper parts of the rather thick cushions in dog 3 were composed of spindle-shaped fibroblasts in radiating arrangement and of hyalin containing scattered foam cells (Fig. 9).

Liver. The liver cells were atrophic. The cords were widely separated by distended sinusoids containing desquamated, swollen, spherical Kupffer cells with foam structure.

Spleen. The pulp of the spleen showed extensive foam-cellular transformation.

Kidney. In the cortex of the kidney the tubules were distended. The

glomeruli were swollen and showed cells with a loose, vacuolar cytoplasm. The edematous interstitial connective tissue contained round cells and multinucleated giant cells.

Testes. The testes were normal in dog 2. The spermatogenic epithelium of the other 2 dogs was markedly degenerated and consisted, in some tubules, of hypertrophic Sertoli's cells only, while in others no epithelial lining was present, but a thickened hyaline capsule surrounded an empty lumen. Some tubules contained deep brown pigmented cells.

Epididymis. The empty ducts of the epididymis were lined by hyperplastic epithelium.

Bone Marrow. The sternum contained fatty myeloid tissue.

g. Methyl Cellulose, 4000 cps. (Three Dogs)

One dog was injected with 2290 cc. of methyl cellulose solution, a second with 3440 cc., and a third with 4930 cc. Autopsies showed that the lungs were edematous and contained some hemorrhagic spots. The livers weighed between 500 and 600 gm., the spleens between 190 and 504 gm. The kidneys were swollen, pale light brown.

Histological examination of the organs gave the following findings:

Brain; Hypophysis; Thyroid and Parathyroid; Pulmonary Artery; Vena Cava; Stomach; Intestine; Pancreas; Bladder. Normal.

Lung. The interalveolar septa were cellular.

Heart. Myocardium and coronary arteries were normal.

Aorta. The aortic intima showed in dogs 1 and 3 a thin foam-cellular proliferation beneath the endothelium. The muscle cells of the media in dog 1 contained fine blue granules or were diffusely incrustated with calcium salts, particularly beneath the intima. There was a more massive foam-cellular intimal proliferation in the ascending aorta of dog 2, associated with imbibition of mucoid material in the media. The other aortic segments were normal.

Large Elastic Arteries. Some scattered small, foam-cellular, intimal proliferations were found, but the majority of the large arteries were normal.

Liver. In the 3 dogs there was an extensive destruction of the liver parenchyma leaving often only a reticular framework and proliferated foam-cellular Kupffer cells.

Spleen. There was extensive necrosis in a foam-cellular pulp in the spleens of dogs 1 and 2, while numerous multinucleated giant cells, arranged in clusters, and massive accumulations of foam cells were present in dog 3.

Adrenals. Some foam-cellular reticulum cells were present in the medulla of the adrenals in dog 2.

Lymph Nodes. The mesenteric nodes of dog 2 showed numerous multinucleated giant cells, mainly in the peripheral sinuses.

Kidney. The renal cortical tubules were distended and lined by a flattened epithelium. The glomeruli were converted into multicystic grape-like formations with foam-cellular endothelium. There were localized round cell infiltrations in the interstitial tissue, associated with foam cells in dog 3.

Uterus. Normal in dog 3.

Testes. The spermatogenic epithelium was highly atrophic and the Sertoli's cells were hypertrophic in dog 2.

Bone Marrow. The sternum contained a dense mature myeloid tissue.

Foam-cellular transformation of the supporting tissue of the choroid plexus of the brain was found only in dogs injected with large amounts of methyl celluloses of 50 and 400 cps., while similar changes in the anterior lobe of the hypophysis were seen in animals treated with large doses of methyl celluloses of 100 and 400 cps. The presence of multicystic, distended pulmonary capillaries and precapillary vessels, lined with multinuclear syncytia and surrounded by large mononuclear cells and foam cells, was noted only in dogs into which methyl celluloses of 50, 100, 400 and 1500 cps. had been introduced. Dogs receiving the two methyl celluloses with lower viscosities and the one with a higher viscosity were free from such lesions. The dogs injected with methyl cellulose of 15 cps. did not exhibit degenerative and foam-cellular vascular reactions, such as were seen in animals treated with methyl cellulose of the other types. Although their occurrence and extent showed a dependence upon the amount of methyl cellulose solution introduced, the foam-cellular intimal response as well as the hyaline and calcifying medial changes were comparatively mild in the dogs which received methyl cellulose of 4000 cps. The livers of dogs treated with methyl celluloses of 15, 25 and 50 cps. showed evidence of direct liver necrosis in the absence of extensive storage of methyl cellulose in swollen, proliferated, foam-cellular Kupffer cells. In dogs injected with the higher molecular methyl celluloses such degenerative hepatic lesions were usually secondary to extensive proliferative reactions in the Kupffer cells, associated with the storage of methyl cellulose in these elements. This type of hepatic parenchymatous destruction was marked in the dogs which received methyl cellulose of 4000 cps. The presence of methyl cellulose within liver cells was noted only in dogs injected with methyl cellulose of 400 cps. In all other dogs the liver parenchyma appeared to be free from methyl cellulose, but sometimes contained fat. The retention of methyl cellulose in the reticulum and reticulo-endo-

thelial cells of the spleen and the transformation of these cells into foam cells and multinucleated giant cells was found in dogs of all series. A similar uniformity was noted in the retention and deposition of methyl cellulose in the glomeruli of the kidneys, in the degenerative changes in the spermatogenic epithelium of the testes, and in respect to the absence of foam cells in the bone marrow.

COMMENT

From the data recorded it becomes evident that the various intravenously injected methyl celluloses elicit, regardless of their molecular weights, changes in the blood characteristic of the hematologic macromolecular syndrome (primary leukopenia, secondary leukocytosis, anemia, increased sedimentation), as well as organic lesions (foam-cellular masses in liver, spleen, adrenal, kidney), typical of the storage of macromolecular colloidal matter, such as glycogen, lipoids, polyvinyl alcohol, silica, pectin, gum arabic, etc., *i.e.*, substances which form emulsions with hemoplasmatic and cytoplasmatic protein solutions.³ However, this reactive pattern was not uniformly developed with all methyl celluloses. If cognizance is taken of those deviations which are attributable to the differences in the amount of material injected, such as the appearance of foam cells in the choroid plexus, in the anterior lobe of the hypophysis, and in the adrenals, there remain discrepancies which seem to be causally related to differences in the physicochemical properties of the injected agents.

The shorter duration of the leukopenia after a single injection of methyl celluloses of 15 and 25 cps., the milder decrease in the number of erythrocytes and in hemoglobin and volume of packed blood cells, the delayed appearance and shorter duration of the acceleration in erythrocytic sedimentation, and the more rapid transitory elevation of the plasma viscosity, as compared to the findings after the introduction of methyl celluloses of higher molecular weights, obviously reflect the influence of the relative molecular size upon the intensity and duration of such acute colloidal reactions. This is particularly true, since a comparatively larger amount of the low molecular methyl celluloses was contained in the injected dose of 40 cc. than was present in solutions of methyl celluloses of higher molecular weight. This conclusion is supported by observations made by Bucher¹³ in connection with the intravenous injection of colloidal solutions of glycogen into rabbits. This investigator found that the severity and duration of the leukopenic reaction was dependent upon the quantity as well as upon the molecular size of the glycogen injected.

However, this relationship concerning the influence of the molecular

size upon the severity and type of reaction was not consistent in respect to the plasmatic viscosity reactions elicited by methyl celluloses of higher molecular weight, as this response was very mild and of very short duration for treatment with both single and repeated doses. The relatively very small absolute amounts used of methyl celluloses of 1500 and 4000 cps. may have militated against any marked and prolonged elevation of the plasma viscosity. On the other hand, it may be possible that the very long-chained molecules of methyl celluloses of 1500 and 4000 cps., when introduced into the blood, do not preserve their rod-shaped form and their directed arrangement responsible for the high viscosity of their aqueous solution, but follow the example of the protein molecules and curl up into globules, thereby causing a marked diminution of the viscous properties. This suggestion is based on a claim of Lepeschkin,¹⁴ who recently reported the occurrence of such changes for the filamentary gelatin molecules when a gelatin solution is heated from just above the jellying point to higher temperatures at which the gelatin is perfectly liquid and much less viscous. An additional causal relation between molecular size and plasmatic viscosity appears to be reflected in the rapid decrease of plasma viscosity after cessation of treatment in animals injected with methyl celluloses of 50 and 100 cps., in contrast to the long-continued elevation of this factor in dogs receiving methyl cellulose of 400 cps.

A similar parallelism between the action of the two low molecular methyl celluloses and the very high molecular cellulose exists in regard to the absence of intracapillary retention cysts of the lungs after their injection. Such lesions were regularly found with the other types. Primary or secondary differences in molecular size and configuration among the various methyl celluloses seem to offer the most plausible explanation for the discrepancies between these anatomical reactions, the development of which depends to a definite degree upon the width of the pulmonary capillaries.

It is noteworthy in this connection that retention of methyl cellulose within the glomerular filter, associated with foam-cellular and proliferative reactions of the endothelium, was found with methyl celluloses of all types regardless of their molecular weights. This is remarkable since three of these substances have a molecular weight below 65,000, which is supposed to represent the critical level for glomerular filtration of macromolecular substances. The observation shows that molecular size determined for the dry material is evidently not the only factor in determining filtrability, but that the degree of molecular hydration plays an important rôle in this respect. Similar results were obtained by Bott and Richards¹⁵ in tests of the permeability of the

glomerular membrane of the amphibian kidney for serum albumin of duck's and hen's eggs, lactoglobulin, zinc insulin, horse serum albumin, tuberculin protein, salmine, and inulin, as only inulin, with a molecular weight of about 6000, filtered through completely. All other agents studied were retained to some degree.

It must remain uncertain whether the molecular weight and perhaps also the molecular configuration of methyl cellulose of 4000 cps. may be responsible for the unusually severe anemia and the extraordinary hyperleukocytosis observed in two of the three injected dogs. Also remarkable is the relatively slight severity and extent of the foam-cellular intimal, and hyalinizing and calcifying medial, lesions of the aorta and large elastic arteries in dogs treated intensely with methyl cellulose of 4000 cps., as compared to the vascular changes in animals treated with methyl celluloses of lower molecular size.

Other striking relations between molecular size of methyl cellulose and biological effect were found in its storage in the liver and in the coagulation time of the blood. Whereas the Kupffer cells and also, after intensive treatment, the histiocytes of the periportal connective tissue of dogs injected with any of the methyl celluloses exhibited a marked foam-cellular transformation and proliferation associated with atrophy of the liver cells and, with the high molecular methyl cellulose, extensive destruction of liver cells, it was only in dogs receiving methyl cellulose of 400 cps. that the liver cells also retained methyl cellulose. It is significant that dogs of this series only displayed a considerable lengthening of the clotting time, while the dogs of all other series showed no abnormal fluctuations of this factor. The presence of hepatic necrosis did not seem to influence the clotting time.

It may be added that the repeated intravenous introduction of methyl cellulose solutions of the different types resulted in the production of vascular lesions characterized by foam-cellular proliferations of the endothelial and intimal cells, sometimes associated with fibroblastic and hyaline intimal thickenings, increased mucoid imbibition of the media which sometimes resulted in the formation of small, irregular, subintimal cavities filled with mucoid material, and with hyalinization and calcification of the media. These various reactions, which increased in extent and degree with the intensity of the treatment, were found in both elastic and muscular arteries but were more marked and more frequent in the former. Although they frequently occurred together, it was not unusual for intimal or medial changes to be seen alone. The vasa vasorum of the aorta sometimes participated in the foam-cellular reactions. It is noteworthy that occasionally extensive areas of medial calcification without intimal lesions or with foam-cellular intimal pro-

liferation were encountered in medium-sized abdominal branches of the aorta. These observations strongly suggest that also in the development of the degenerative intimal and medial lesions in man, particularly those of the Mönckeberg type, common causal factors are active, and that medial calcinosis of the peripheral arteries does not represent a special type of vascular disease which must be distinguished etiologically from ordinary atherosclerosis.¹⁶⁻¹⁹

The high frequency of severe testicular atrophy in the dogs of this experiment supports the conception advanced in previous publications that anoxemia is the fundamental common causal factor in the production of degenerative vascular disease, as testicular degenerations are a phenomenon frequently met with in anoxemic states (chronic mountain sickness, lead poisoning, nitrate poisoning, nicotine poisoning, carbon disulfide poisoning, carbon monoxide poisoning, etc.)^{17, 20}

CONCLUSIONS

1. The intravenous injection of single and repeated doses of seven types of methyl cellulose ranging in molecular weight from 32,200 to 143,000 results in hematic and organic reactions which differ among themselves in some respects, depending upon the molecular weights.

2. Methyl celluloses of low molecular weight cause a shorter duration of a transitory leukopenia, a milder decrease in the number of erythrocytes, a shorter acceleration of erythrocytic sedimentation and a shorter elevation of the plasmatic viscosity than those elicited by methyl celluloses of higher molecular weights.

3. Methyl celluloses of high molecular weight form an exception to the rule in regard to the increase in plasmatic viscosity, as they do not elicit an appreciable elevation of this factor even after the introduction of large amounts.

4. A similar parallelism between molecular weight and anatomical lesions is represented by the fact that the two methyl celluloses of lower molecular weight do not produce intracapillary pulmonary retention cysts, as do all other methyl celluloses with the exception of the methyl cellulose of highest molecular weight.

5. All methyl celluloses were retained at least in part by the glomerular filtration membrane, indicating that here the degree of hydration plays an important rôle by influencing molecular size.

6. Lengthening of the clotting time was found only with methyl cellulose of 400 cps., which has about the same molecular weight as serum albumin and enters the liver cells, which do not store the other methyl celluloses.

7. The degree and distribution of atheromatous intimal, and hyalin-

izing and calcifying medial, lesions in the elastic and muscular arteries increased with the intensity and duration of treatment, but varied somewhat with the type of methyl cellulose injected, being least developed with the very high molecular type.

8. The frequent occurrence in muscular arteries of medial calcification unrelated to atheromatous changes indicates that the same causative mechanism is active in the production of both intimal atheromatosis and medial calcinosis.

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[Illustrations follow]

DESCRIPTION OF PLATES

PLATE 141

- FIG. 1. Myocardial necrosis and calcification with proliferation of fibroblasts and with infiltration of leukocytes and mononuclear cells. An artery shows considerable proliferation of intimal foam cells. Hematoxylin and eosin stain. $\times 360$.
- FIG. 2. Large elastic artery with mild foam-cellular proliferation of the intima and a large focus of necrosis and calcification in the middle media. Hematoxylin and eosin stain. $\times 360$.

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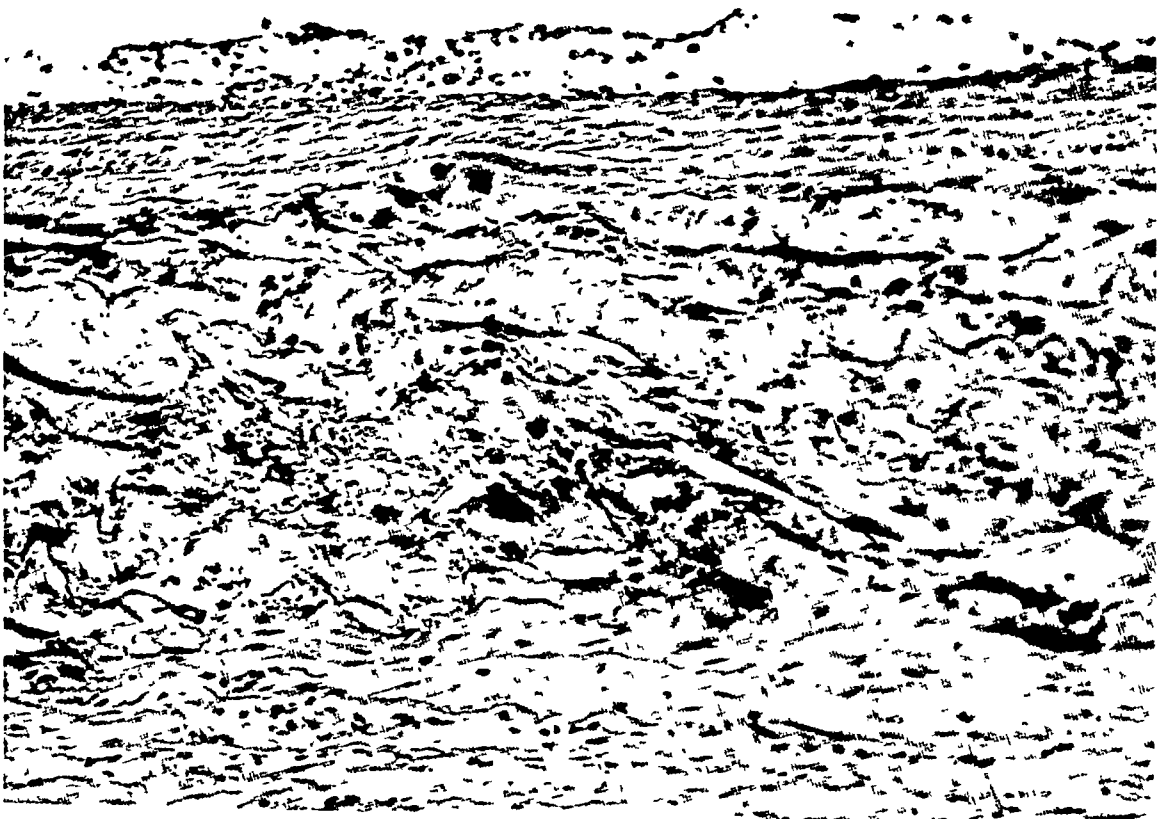
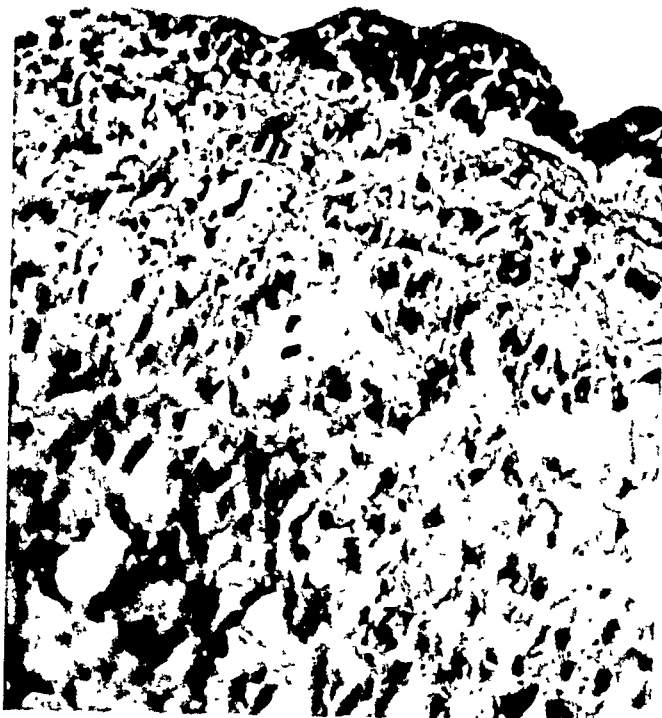
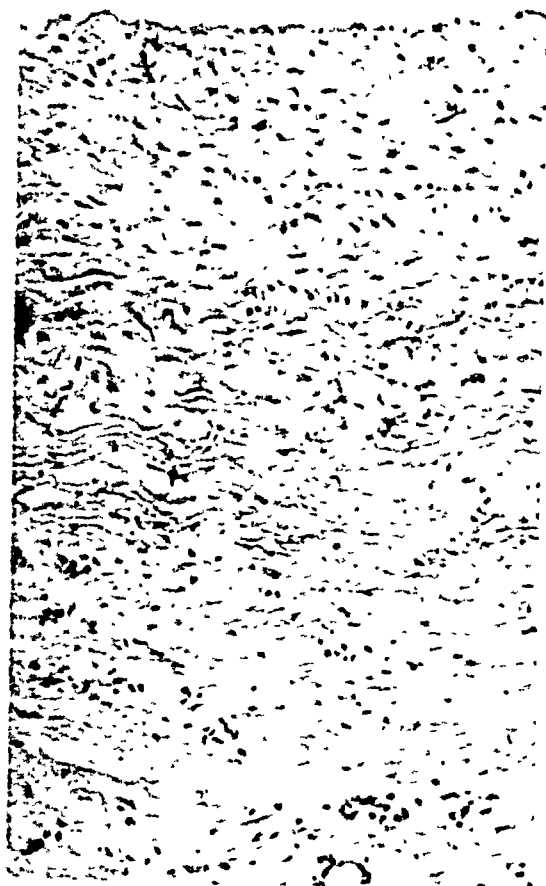


PLATE 142

- FIG. 3. Extensive area of fibrosis and hyalinization in the outer half of the aortic media (lower part of figure) with marked capillary proliferation and mild infiltration with lymphocytes. Hematoxylin and eosin stain. $\times 310$.
- FIG. 4. Cushion-like, cellular intimal thickening of the aorta with invasion of scattered leukocytes into a highly mucoid media. Hematoxylin and eosin stain. $\times 310$.
- FIG. 5. Uterine arteries with extensive foam-cellular intimal proliferation almost occluding the lumina. Hematoxylin and eosin stain. $\times 360$.

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Hueper

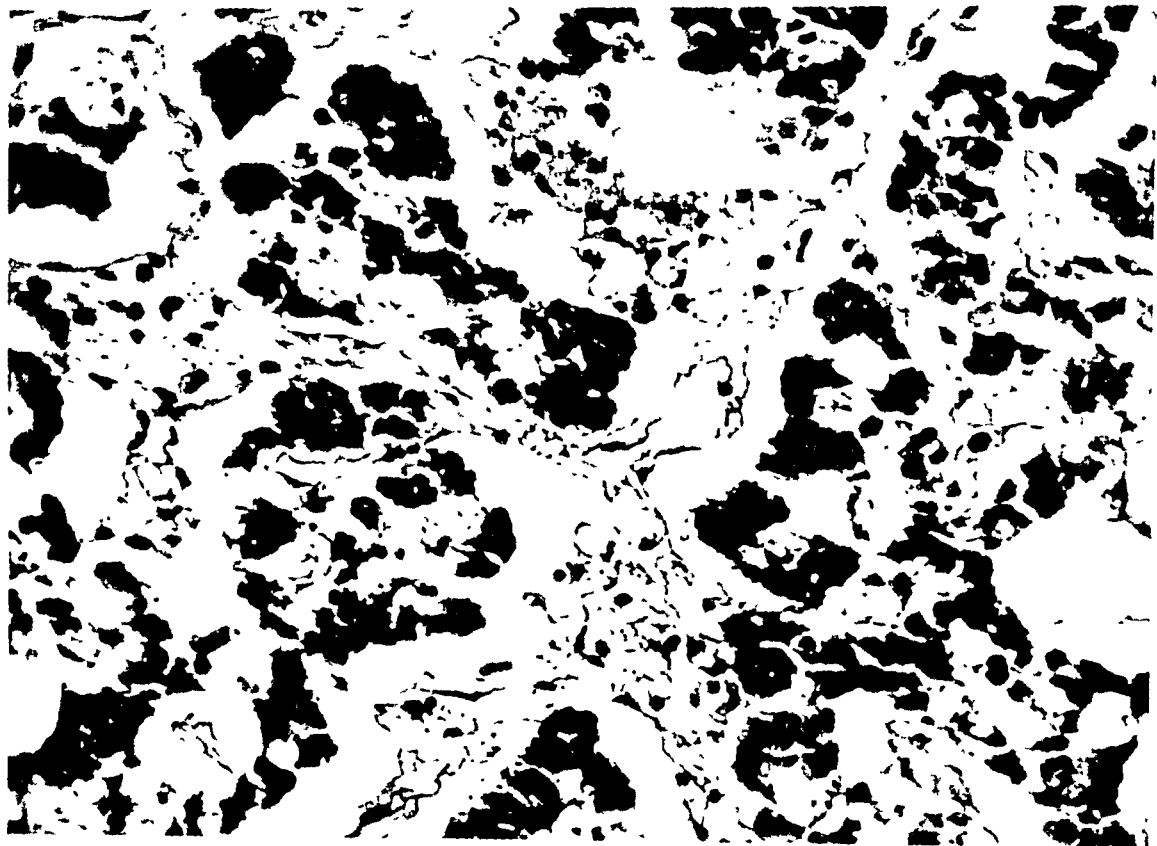
Intravenous Injections of Methyl Celluloses

PLATE 143

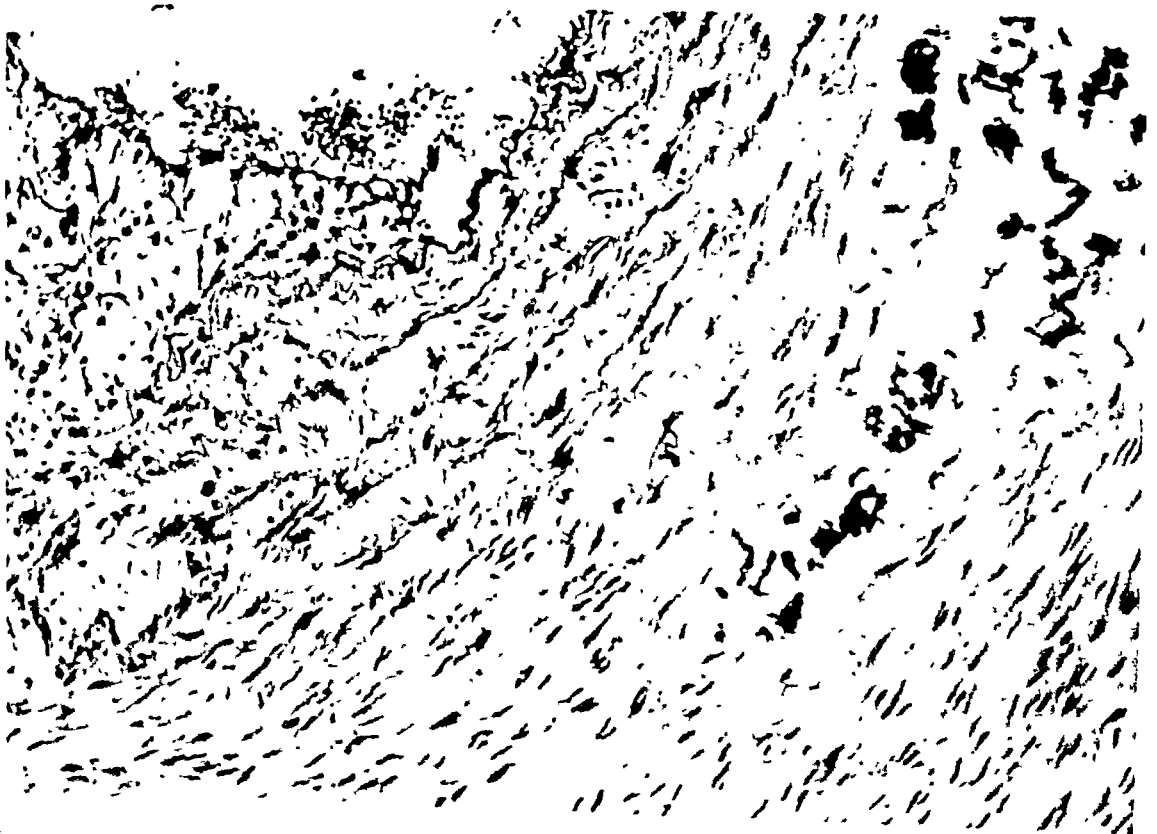
FIG. 6. Anterior lobe of the hypophysis with foam-cellular interstitial tissue. Hematoxylin and eosin stain. $\times 660$.

FIG. 7. Pulmonary artery with foam-cellular thickening of the intima and with hyalinization and calcification of the media. Hematoxylin and eosin stain. $\times 360$.

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Hueper

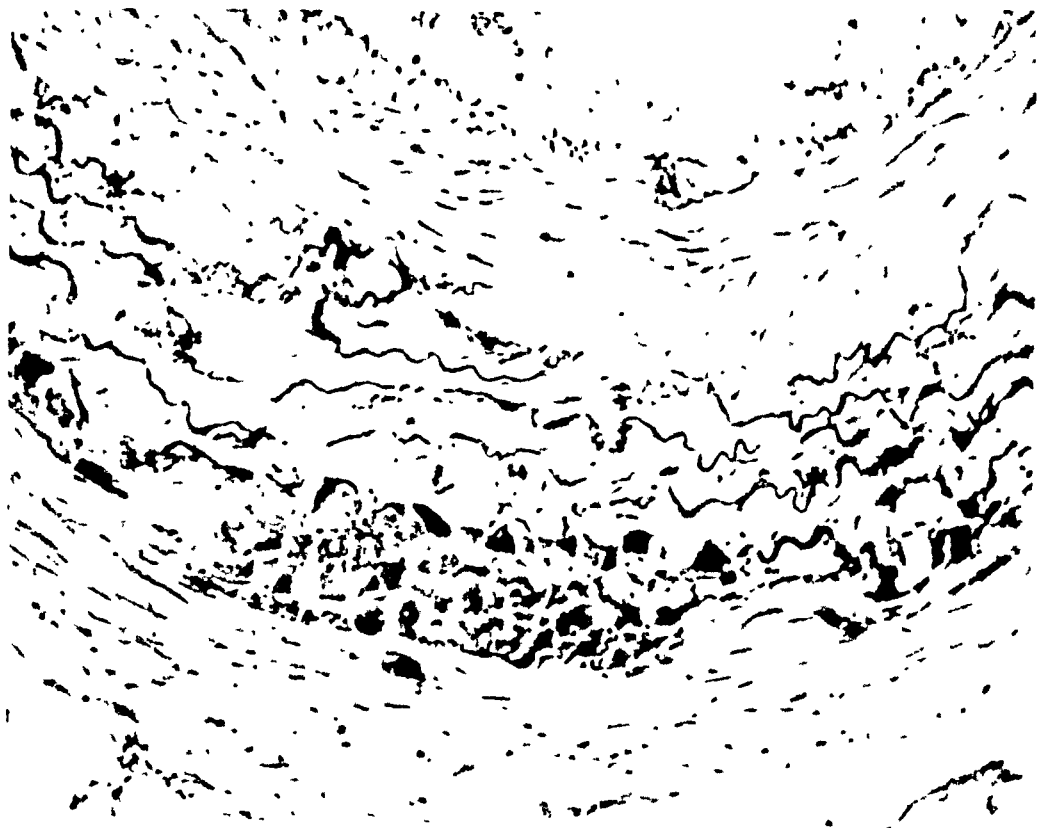
Intravenous Injections of Methyl Celluloses

PLATE 144

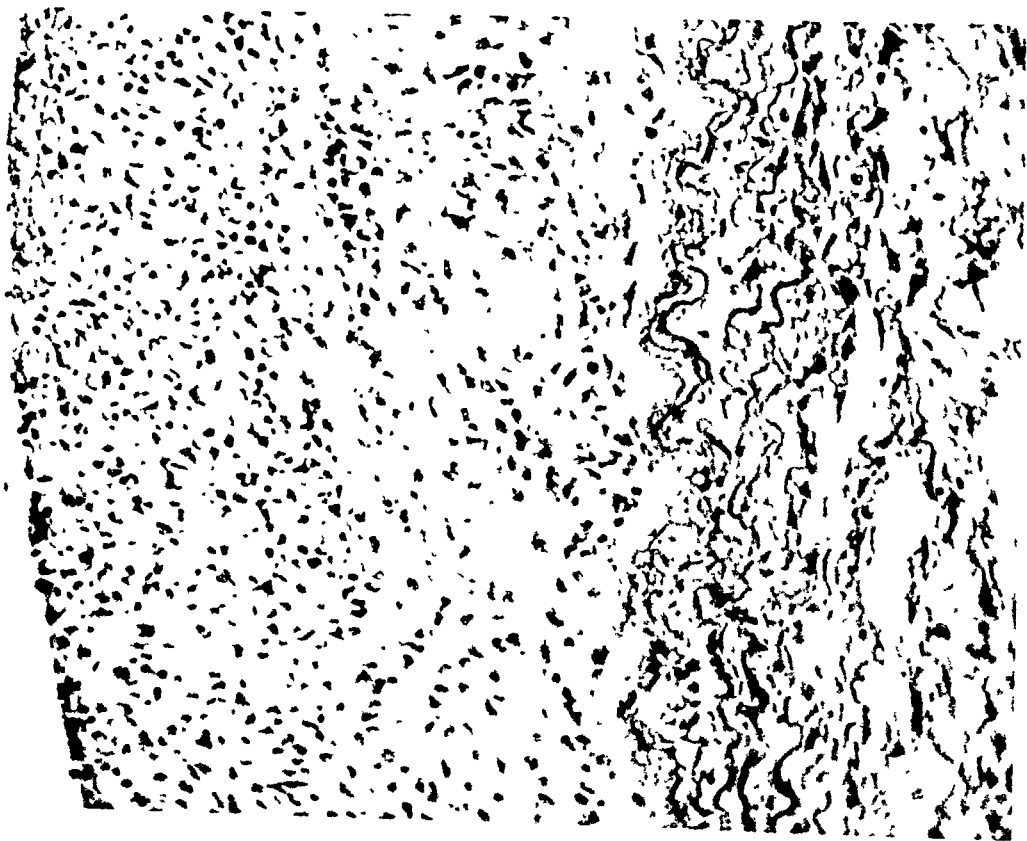
FIG. 8. Large muscular artery with extensive medial necrosis, and calcification of the necrotic matter and of the elastic fibrils. Hematoxylin and eosin stain. $\times 360$.

FIG. 9. Intimal thickening of the aorta consisting of a foam-cellular inner layer and a deeper, partly hyaline, partly fibroblastic layer covering a highly mucoid media. Hematoxylin and eosin stain. $\times 360$.

8



9



Hueper

Intravenous Injections of Methyl Celluloses

SPONTANEOUS AND TRANSPLANTED RETICULUM CELL SARCOMAS IN WISTAR RATS *

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Within the past year, 14 spontaneous sarcomas of lymphatic tissue were found in a group of rats comprising 1000 Wistar albinos and 185 gray Norways, maintained for studies in problems of aging in The Wistar Institute animal colony. Five of the tumor-bearing rats were of the gray Norway strain (2 males and 3 females, ranging in age from 370 to 670 days), and 9 were of the Wistar albino strain (3 males and 6 females, ranging in age from 331 to 555 days). Three of the albino rats had been splenectomized. Approximately 67 per cent of the rats of the entire group were as old or older than the youngest tumor-bearing member. The neoplasms were diagnosed as reticulum cell sarcomas, and were successfully transplanted.

GROSS APPEARANCE OF SPONTANEOUS TUMORS

Ascites was always present; more than 40 cc. of cloudy, bloody fluid could be withdrawn from the abdominal cavity. The largest tumors occurred in the omentum and in the mesentery at the ileocolic junction. They consisted of small semitranslucent bodies or of larger, irregular, lobulated masses, which were partially hemorrhagic. A similar growth was found at the site of the thymus in all but four rats. In advanced stages, the mediastinal, renal, pelvic and retroperitoneal lymph nodes were involved. The axillary, inguinal and cervical lymph nodes were invaded in one albino rat.

In one of the gray Norway rats multiple tumorous growths studded the diaphragm and abdominal walls. Microscopical sections of the intestine showed evidence of invasion of the muscles but not of the mucosa (Fig. 1). In the majority of the tumor-bearing rats, part of the pancreas was replaced by neoplastic tissue, and in three instances the liver was infiltrated. Other organs appeared to be normal, and the neoplasm was not found in the spleen, kidneys, adrenals, lungs, or gonads in microscopical preparations.

CELLS OF SPONTANEOUS TUMORS

The neoplasm was composed of closely packed, large mononuclear cells, usually round or oval in shape, and several times the diameter of a normal lymphocyte. The nuclei were sharply outlined, and were for

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the most part vesicular, containing one or two prominent nucleoli. Mitoses were common. The amount of finely granular cytoplasm varied in each cell, but tended to be scanty. A microscopical section through one of the tumors is shown in Figure 2.

In silver-stained preparations, for which we are indebted to the Army Medical Museum, "a delicate reticulum is seen to enmesh the cells in some parts of the tumor; in other areas the growth is solidly cellular and lacks stroma of any kind (Figs. 5 and 6). This variation is interpreted as signifying that in the older parts of the tumor reticulum has been formed, while the cells of rapidly growing parts have not as yet elaborated reticulum fibrils." *

TRANSPLANTATIONS

The first transplantation of a spontaneous tumor from an albino (444 days old) into rats of the same strain failed to grow in either of the recipients. The second transplanted spontaneous tumor (also from an albino, 531 days old) has been carried successfully through thirteen passages in Wistar albino rats. Thirty-one rats received implants, some subcutaneously and some intraperitoneally, and the tumor grew in 29 of them. The recipient rats ranged in age from 16 to 81 days when implanted. They were not related to the original donor, but the majority of them were bred from the littermates of rats that had proved to be susceptible in early passages. Our results show that the younger the recipient the more readily the tumor grew. Regardless of the site of implantation, the resulting neoplasm usually resembled the spontaneous tumors.

In some of the rats receiving grafts the tumor grew subcutaneously at the point of entrance of the trocar. In one of these the neoplasm remained localized. After 64 days it measured 50 by 42 by 25 mm. Intraperitoneal growth, as seen in the other hosts, was characterized by ascites, rapid spread and enlargement of the tumor, and early death. A rat 81 days old when inoculated died after 73 days, but in younger hosts abdominal tumors caused death in 20 days on the average.

Cells from the body fluids and pieces of the sarcomas engrafted into the abdominal cavity of young rats produced discrete, often hemorrhagic nodules, principally in the omentum but also in the mesentery, in the form of beads paralleling the intestine. If the host survived long enough, the smaller growths coalesced into masses characteristic of the spontaneous tumors. Figure 7 illustrates an early stage in the fusion of small tumors, in which the outlines of the individual nodules are discernible.

*Quoted from a letter from Col. J. E. Ash in regard to U. S. Army Medical Museum Accessions nos. 91454 and 91258 a and b.

In rats receiving grafts, usually a greater number of abdominal lymph nodes were affected, and more extensively, than in rats in which the tumor occurred spontaneously. Growths of the malignant cells occurred in the thoracic cavity of the majority of the treated rats. Invasion of the liver and the pancreas (Fig. 3) was observed, but not of spleen, kidneys, adrenals, lungs, or gonads. However, inoculation of a fine suspension of tumor cells directly into spleen and kidney produced typical growths within these organs.

Microscopically the cells of tumors that arose from grafts appeared to be identical with those of the spontaneously occurring sarcomas (Fig. 4). In the more recently developed masses reticulum was lacking, but in the older parts of the tumor a well developed reticulum enmeshed the cells (Figs. 5 and 6).

MALIGNANT CELLS FOUND IN BODY FLUIDS

Routine cell counts of peripheral blood from nine inoculated rats and four with spontaneous neoplasms were made before the animals were sacrificed. In one of the former, the red cell count was 2,370,000 cells per cmm.; and in one of the latter, 4,680,000 cells per cmm. Erythrocyte counts in the other rats averaged 6,818,000 per cmm. White cells ranged from 4,950 to 21,900 per cmm., the higher number occurring in an older rat with only subcutaneous tumors; the average was 9,330 per cmm. The differential blood counts were for the most part within the usually accepted normal ranges for rats; ¹ averages were: neutrophils, 26.8 per cent; lymphocytes, 72.2 per cent; monocytes, 0.5 per cent; eosinophils, 0.4 per cent; basophils, 0.1 per cent. Large lymphocytes were frequently noted. One malignant cell, conspicuous among the smaller normal cells, was recognized in two spreads. With Wright's stain the large round nuclei were lavender and finely granular, and the narrow rim of cytoplasm a deep blue. A section of a buffy coat of centrifugalized blood presented an aggregate of malignant cells that closely resembled a formed tumor.

Examination of ascitic fluid from tumor-bearing rats revealed an abundance of malignant cells, indistinguishable from those seen in blood smears, many of which were in mitosis. In a spread of ascitic fluid the size of the enlarged cells was three to five times that of normal lymphocytes. Numerous mast cells and eosinophils also were present.

Intraperitoneal injections of the following substances were made from tumor-bearing hosts into healthy young albinos: blood plasma (into five rats), blood cells (four rats), whole blood (five rats), cells from ascitic fluid (three rats), and ascitic supernatant fluid (into four rats). Typical sarcomas appeared after inoculation of the cells but not following injections of cell-free material. The failure to produce tumors

by the injection of plasma and cell-free ascitic fluid indicates that the causative factor of this tumor is not a virus.

DISCUSSION

A tumor, occurring spontaneously in 14 of the rats of the Wistar colony devoted to study of aging, has been identified as a reticulum cell sarcoma. Grossly, it conforms to McEuen's² description of spontaneous lymphosarcomata that occurred in a colony of hooded rats. It resembles the lymphosarcomata studied by Curtis and Dunning³ except that in our rats perforation of the gut was not found and malignant growths frequently occurred in the thoracic cavity. The tumor seems to resemble closely the reticulum cell sarcoma described by Jenney,⁴ although we have not found the invasion of spleen, kidneys, or lungs, or the leukocytosis following implantation, that she noted.

The location of the early sarcomas in the mesenteries suggests that some element in the absorbed food might induce tumor formation, particularly as the rats used by McEuen² and by Jenney⁴ were fed the same diet as our animals. However, in another group of gray Norway and albino rats, raised in the Wistar colony under the same conditions and on the same diet as those reported here, reticulum cell sarcomas were not observed, although routine autopsies were not performed.

Nelson and Morris,⁵ reporting a reticulum cell lymphosarcoma in rats which differed from ours in the location of the original growth, ruled out pulmonary infection as an apparent cause of the neoplasm. In the rats of Curtis and Dunning,³ ulceration of the gut was common but did not invariably accompany the neoplasm. We, too, found no indication of a relation between infection, or any other disorder, and the spontaneous reticulum cell sarcomas. Pathological conditions other than the neoplasms themselves were not observed. Perforation or ulceration of the gut was not found, and necrosis in tumors was not constant. Tissue cultures of the sarcomas, made at The Wistar Institute, were free of bacteria.

SUMMARY

1. A spontaneous reticulum cell sarcoma was found in three female and two male gray Norway rats, 370 to 670 days old, and in six female and three male Wistar albino rats, 331 to 555 days old, in a group of over 1000 animals.

2. The neoplasm occurred in the mesentery and in the omentum, and was found frequently in the thoracic cavity and occasionally in abdominal lymph nodes and liver, but not in other organs. Ascites accompanied the growth of the tumor.

3. The spontaneous tumor in one Wistar albino rat, 531 days of age,

was successfully transplanted into 2 young rats of the same strain. The transplanted tumor was carried through thirteen successive passages, and tumors resembling the spontaneous sarcoma developed in 29 of the 31 rats engrafted during these passages.

4. Subcutaneous implants grew slowly and tended to remain localized. Grafts in the abdominal cavity spread quickly and caused death of the hosts in an average of 20 days.

5. The cells of spontaneous and implanted tumors were indistinguishable. Reticulum was found only in older growths of both the spontaneous and the engrafted sarcomas.

6. Malignant cells were identified in the blood and ascitic fluid of tumor-bearing rats. Intraperitoneal injection into healthy young albino rats of the centrifugalized cells from these fluids produced typical sarcomas; injection of plasma and cell-free ascitic fluid did not produce tumors.

We wish to express our sincere appreciation to Dr. Margaret Reed Lewis for her aid and direction; and to Dr. George W. Corner of the Carnegie Institute of Washington for help with some of the photographs. We also wish to thank Col. J. E. Ash, Curator, and Lt. Col. Balduin Lucké of the Army Medical Museum, Institute of Pathology, for their interest and cooperation in the identification of the tumors, and for their kindness in furnishing two of the photographs used in this paper.

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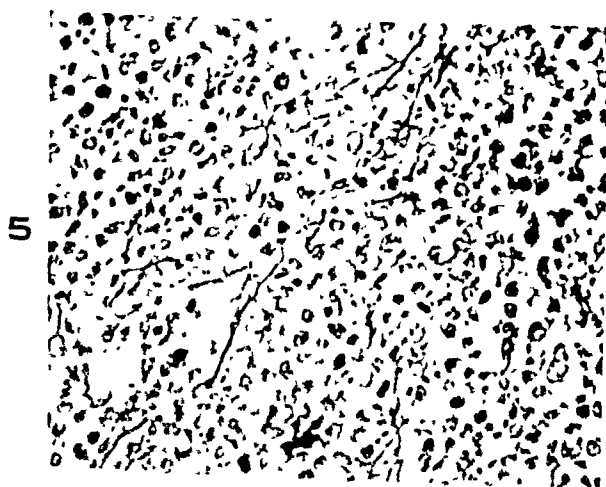
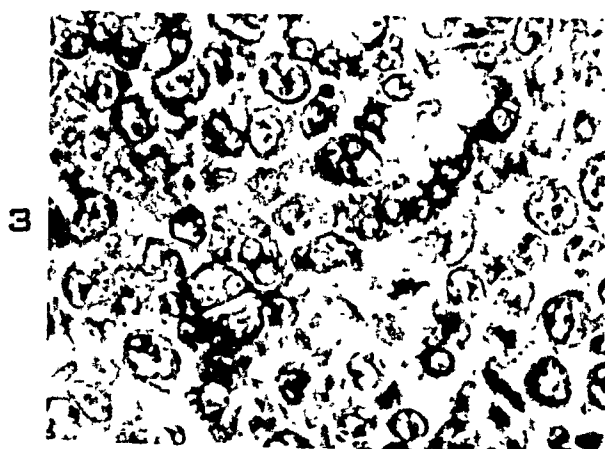
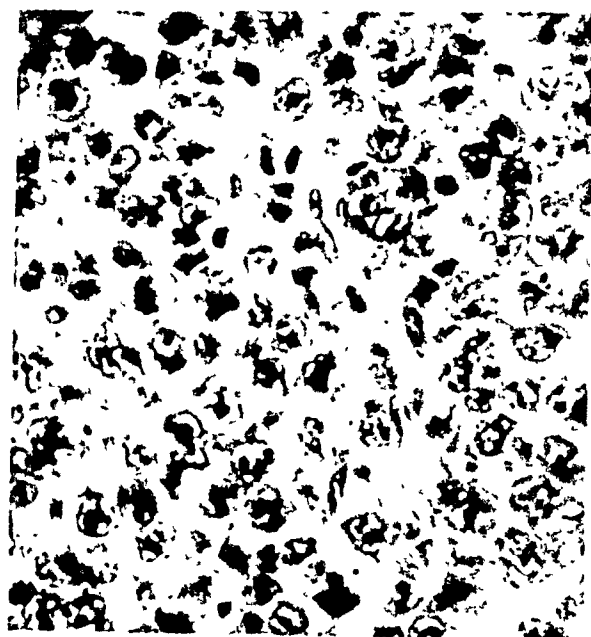
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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 145

- FIG. 1. Muscle wall of intestine invaded by cells from an adjacent tumor in the mesentery. $\times 189$.
- FIG. 2. Section of a spontaneous reticulum cell sarcoma. $\times 472$.
- FIG. 3. Invasion of pancreatic tissue by sarcoma cells. $\times 472$.
- FIG. 4. Section of reticulum cell sarcoma from a recipient rat. $\times 472$.
- FIG. 5. Silver-stained section of young tumor showing small amount of reticulum. $\times 212$. (U. S. Army Medical Museum Neg. no. 76210. Acc. no. 91258a.)
- FIG. 6. Heavily stained, abundant reticulum in older tumor. $\times 212$. (U. S. Army Medical Museum Neg. no. 76209. Acc. no. 91258a.)



Farris and Yeakel

Reticulum Cell Sarcomas in Wistar Rats

PLATE 146

FIG. 7. Widespread development of reticulum cell sarcoma in a recipient rat.

- (a) Subcutaneous tumor at the site of inoculation.
- (b) Tumor in the thoracic cavity.
- (c) Spleen.
- (d) Tumor in the omentum.
- (e) Nodules in the mesentery by the small intestine.
- (f) Growths in the connective tissue by the gonads.



Farris and Yeakel

Reticulum Cell Sarcomas in Wistar Rats

NONSUPPURATIVE NODULAR PANNICULITIS (WEBER-CHRISTIAN'S DISEASE)*

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Weber-Christian's disease is a clinicopathological entity characterized by recurring episodes of fever and the occurrence of numerous, painful, slightly tender, subcutaneous nodules. These nodules consist of nonsuppurative areas of inflammation and necrosis in the subcutaneous fat. In only 2 of the 24 cases reported in the literature was death apparently due to the disease. In one of these cases a necropsy was performed and reported by Kritzler.¹ The literature on the reported cases is adequately reviewed by Bailey.² The object of this report is to present an additional case with necropsy. The patient reported upon here, although dying in uremia as a result of chronic glomerulonephritis, was in the active phase of nonsuppurative nodular panniculitis.

REPORT OF CASE

P. F., an unmarried Irish male, 51 years old, was admitted to the First Medical Service at Bellevue Hospital on July 12, 1941. The chief complaint consisted of generalized aching pain involving all of his muscles. This was of 1 week's duration. The patient had a previous history of three admissions for alcoholism to the Psychiatric Division of this hospital. The last admission was 5 years prior to the present illness. Three days before the present admission he also complained of passing black stools with flecks of red blood and the following day there were two episodes of epistaxis. Due to the patient's mental state, reliable personal and family history could not be obtained.

On admission the temperature was 98.6° F.; pulse, 80; respirations, 20; blood pressure, 140/100 mm. of Hg. The patient was drowsy, slightly confused, but co-operative. Speech was thick and slurred. No abnormalities of the skin were noted at this time other than a few areas of ecchymosis over the right tibia. Except for some abdominal tenderness in the right upper quadrant, there were no other significant findings on physical examination.

Two days after admission several small subcutaneous, pea-sized nodules were noted in both arms and legs. These were slightly tender and freely movable beneath the skin. The overlying skin showed no changes. At the same time the patient began to have an irregular fever ranging between 99° and 104° F.

Laboratory examinations at this time revealed the following: red blood cells, 3,500,000; hemoglobin, 8.5 gm.; white blood cells, 8,500; polymorphonuclear leukocytes, 85 per cent; lymphocytes, 15 per cent. Platelets were within normal range. No eosinophils were seen. Specific gravity of the urine, 1.010 and 1.016; albuminuria, 1 to 2 plus and occasional granular casts. Blood nonprotein nitrogen, 182 to 275 mg. Phosphatase, 4.3 Bodansky units. Albumin-globulin ratio, 4.1/2.0. Carbon dioxide combining power varied between 20 and 52. Cephalin-flocculation test, 2 plus. A stool contained bright red blood. Wassermann reactions on blood and spinal fluids were negative. Roentgenograms of thorax and abdomen revealed no abnormal-

* Received for publication, September 21, 1943.

ities. Serum agglutination tests were negative for typhoid and paratyphoid bacilli and *Brucella melitensis*. Skin tests with trichinella antigen were also negative.

One of the subcutaneous nodules was removed with the surrounding adipose tissue. The specimen measured 2 by 1 by 1.5 cm. In the central portion of this mass was a somewhat firm, palpable nodule that on section appeared yellowish gray. Radiating streaks of this yellowish gray material extended from the central area into the adjacent fat. Histologically the nodule was an area of fat necrosis with a surrounding infiltration of lymphocytes, occasional polymorphonuclear leukocytes and numerous fat-laden macrophages. There was a moderate increase of fibrous tissue immediately adjacent to this lesion. Scarlet R stain showed material within the phagocytic cells to be fat. A diagnosis of nonsuppurative nodular panniculitis (Weber-Christian's disease) was made.

The patient's condition became steadily worse. He eventually went into uremic coma and died 10 days after admission. During this period, however, some of the nodules first noted seemed to disappear or, at least, to become reduced in size.

Necropsy Findings

The subcutaneous fat was examined carefully and several of the nodules previously described were found. Similar nodules were found also in the mesenteric, omental and pretracheal fat deposits. These nodules were 2 to 5 mm. in diameter and varied from dull gray to yellowish gray. The kidneys were reduced in size, had a granular surface and the cortex was reduced in width with striations blurred and poor differentiation from the medulla. The liver was of the usual size, somewhat flabby and yellowish in appearance.

Histological Examination. The nodules in the fat were of varying appearance. The earliest and smallest lesions consisted merely of small accumulations of fat-laden macrophages (Fig. 1). Lesions somewhat larger had small central areas of necrosis (Fig. 2), about which were lymphocytes, polymorphonuclear leukocytes and numerous fat-laden macrophages (Fig. 3). In the obviously older nodules the necrotic material was decreased and the inflammatory cells had been replaced by fibrous tissue (Fig. 4).

The alterations in the kidney were characteristic of the end stage of chronic glomerulonephritis. Numerous fat droplets were contained within the liver cells. Small areas of fat necrosis were present about the pancreas. These had the appearance characteristic of pancreatic fat necroses and did not resemble the necrotic nodules in the subcutaneous tissue.

The final diagnosis was chronic glomerulonephritis with uremia, nonsuppurative nodular panniculitis, pancreatic fat necrosis and fatty change of the liver.

COMMENT

In the case reported by Kritzler,¹ the characteristic lesions were limited to the subcutaneous fat. However, fat emboli were found in the lungs and there was widespread acute necrosis of the liver and spleen.

The liver showed fatty change. In the case presented in this report characteristic necrotic areas were found not only in the subcutaneous fat but in the mesenteric, omental and pretracheal fat. There were no fat emboli in the lungs. Areas of necrosis in the liver and spleen were not observed. However, foci of fat necrosis were present about the pancreas.

The relationship of this change in the peripancreatic fat to nonsuppurative panniculitis is not clear as the two lesions had very dissimilar histological compositions. Since the patient was a chronic alcoholic, the peripancreatic fat necrosis may have been on this basis. Fatty change in the liver was present in this case as well as in the case reported by Kritzler.¹

It was also possible to study the various lesions from their apparent incipency to their more advanced and apparently healed stages. The findings were in agreement with those in the case reported by Shaffer³ in which the earliest lesion had been described as consisting of small collections of lipid-containing macrophages. The lesion in our case was soon followed by nonsuppurative necrosis which became more extensive and infiltrated with lymphocytes, polymorphonuclear leukocytes and an occasional multinucleated giant cell. The lesion finally showed fibrosis (Figs 1 to 4).

Questions concerning the etiology and the relationship to the co-existing conditions present in this case must remain unanswered. There was no history of bromide or iodine ingestion as has been reported in some of the cases. Sulfathiazole was given after the appearance of these nodules and, therefore, could not bear any causal relationship. The areas of purpura, associated with uremia in this case, were for the most part unrelated in position to the characteristic nodules.

SUMMARY

1. A second case of Weber-Christian's disease with necropsy is presented.
2. Characteristic lesions were present in the mesenteric, pretracheal and omental fat, in addition to those in the subcutaneous adipose tissue.

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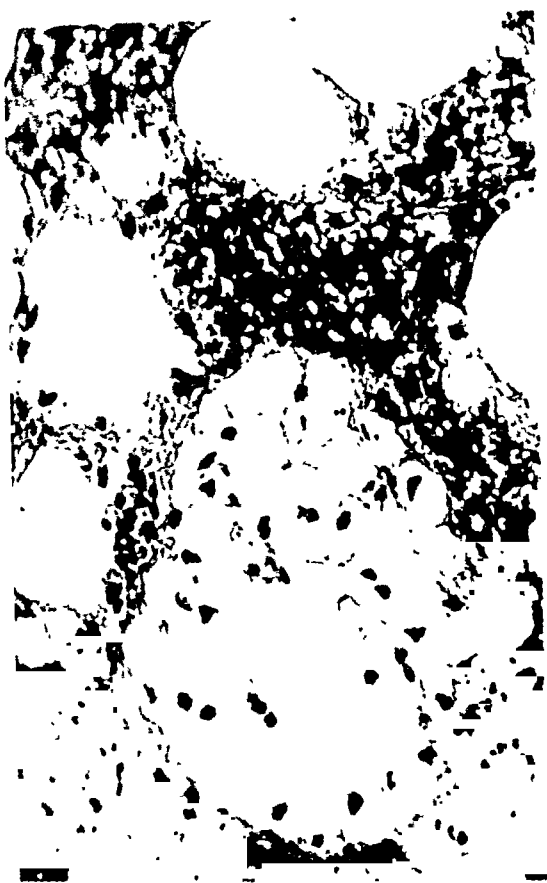
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DESCRIPTION OF PLATE

PLATE 147

- FIG. 1. Section through an early lesion showing a collection of fat-laden macrophages. Trichrome stain. $\times 320$.
- FIG. 2. Section through a nodule in the pretracheal fat showing a small necrotic area. Hematoxylin and eosin stain. $\times 40$.
- FIG. 3. Section of the nodule in the mesenteric fat showing fat-laden macrophages. Hematoxylin and eosin stain. $\times 320$.
- FIG. 4. Section through an older nodule showing fibrosis. Hematoxylin and eosin stain. $\times 130$.

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Spain and Foley

Nonsuppurative Nodular Panniculitis

MULTIPLE PRIMARY LIPOSARCOMAS *

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Adipose tissue should be considered as an organ subject to its own diseases. Wells¹ stated it very well: "Adipose tissue is not merely a common connective tissue loaded with stored simple fats but, to a large extent, structurally, developmentally and functionally an independent special tissue more after the order of the true ductless glands." We see systemic diseases such as von Recklinghausen's neurofibromatosis, lymphosarcoma, plasma cell myeloma, and others fairly frequently. It seems reasonable, therefore, that fat tissue, behaving as a single organ, could be involved by a malignant process.

True liposarcomas are certainly rare,² and the occurrence of multiple primary liposarcomas is practically unknown in this country. The European literature, however, offers four articles on this subject which will be reviewed later.³⁻⁶ Liposarcomas can occur in any area in which fat is normally found, but arise most frequently in the popliteal spaces, the areas about the buttocks, and in the retroperitoneal areas. They often appear encapsulated, but it is probable that this encapsulation is false, as recurrences after surgery are common.

The following case demonstrates the appearance of multiple primary malignant fatty tumors which were located in the adipose tissue, grew with varying speeds, recurred in some areas, and finally caused death after 10 years.

REPORT OF CASE

F. M. (E. F. S. C. H. no. 3281), a white male, 54 years old, was admitted to the hospital on September 18, 1941. In 1933, a lump in the right inferior gluteal fold had been noted, and in 1938 it was removed at the Bell Memorial Hospital in Kansas City. It shelled out easily. One and one-half years before admission to this hospital, the patient fell, striking his left hip, and 6 months later a hard, painless swelling above the left hip bone was felt. This grew slowly. For 1 year prior to admission, there had been pain on the outer surface of the left thigh radiating down to the foot. Four months previous to admission, he noticed a lump in the right popliteal space. Weakness of the legs had been marked for 2 weeks. Physical examination revealed a well developed white male who was quite weak, preferring to lie in bed. On examination of the abdomen, there was a large, smooth, firm mass felt in the right lower quadrant just beneath the iliac crest. In the left lower quadrant, there was a similar but smaller mass. In the soft tissues of the back, just above the iliac crest on the left, there was a smooth, round, elevated tumor mass measuring about 20 cm. in diameter and elevated about 6 cm. above the surrounding skin (Fig. 1). It was not ulcerated or attached to the overlying skin. There were also several small nevi and one *café-au-lait* spot. The extremities showed signs of wasting and the tendon reflexes were absent. These changes were thought

* Received for publication, September 29, 1943.

to be due to pressure on nerves by the large abdominal masses. Just beneath the right popliteal fossa in the soft tissues, there was a smooth, round, movable mass measuring about 8 cm. in diameter. Roentgenograms following a barium enema showed displacement of the cecum, proximal ascending colon and terminal ileum by an extrinsic, homogeneous tumefaction of the right lower quadrant.

On October 3, 1941, the tumor in the popliteal space was excised; on October 31st the mass on the back was resected; on December 6th the abdominal mass was incompletely resected. The patient was discharged from the hospital on December 24th. He was readmitted on February 14, 1942, because of recurrence of the tumor in the retroperitoneal space. This was given intensive x-ray therapy totaling 7600 r. over four large fields, but the tumor regressed only slightly. He was discharged from the hospital on April 7th. He returned on June 6th, much worse. In the right supraclavicular fossa, there was a hard, movable mass about 5 cm. in diameter, which was removed. After this, he returned to a county home, gradually lost strength, and died on November 23, 1942.

All of the surgically excised tumors had many similar characteristics. They varied in size from 75 gm. (popliteal space) to 1200 gm. (retroperitoneal space). They were all in the soft tissue and shelled out easily. Their external surfaces were lobulated, and showed numerous convolutions. In the grooves formed by these convolutions ran a fine network of small blood vessels. On section, they cut with varying degrees of resistance depending on the amount of connective tissue present. The first one removed cut the easiest and looked very much like brain tissue. Its appearance conformed to Shaw's⁷ description of liposarcoma. All of the specimens showed varying degrees of hemorrhage and necrosis relative to the cellularity and vascular supply.

Autopsy

Anatomic diagnoses. Multiple primary liposarcomas, arising from the subepicardial, mediastinal, mesenteric, peritoneal, retroperitoneal, subcutaneous, and bone marrow fat; metastatic liposarcoma of the liver.

The body was emaciated and showed numerous well healed surgical scars. There was a residual, soft tissue tumor of the right thigh measuring about 10 by 8 by 4 cm., and another in the soft tissue of the right popliteal space. At the initial incision, tumor was found in the second and third costal interspaces, apparently prolongations of a tumor arising from the mediastinum. In the peritoneal cavity, the small intestines were adherent to the lower half of the abdominal wall. The liver was rotated counter-clockwise about 90 degrees, so that the normal superior aspect was lying on the right side of the body. As a whole, the liver was lying in the left upper quadrant, displaced and rotated by a large mass of neoplastic tissue occupying the normal liver space. On the surface of the liver were several sharply delineated, yellowish white nodules measuring from 1 to 6 cm. in diameter. On

section they were soft, circular and projected slightly above the cut surface. Tumor completely filled the right iliac fossa and right lumbar gutter and was covered by the iliopsoas muscle. In the left lower quadrant, a similar mass of firm, grayish yellow neoplastic tissue incompletely filled the left iliac fossa. Lymph nodes were apparently replaced by tumor and measured up to 2 cm. in diameter. The right pleural cavity contained a large mass of soft, friable neoplastic tissue which filled one-half to two-thirds of the space, compressed the lung, pushed its way through the intercostal spaces, and caused deviation of the mediastinum to the left. The left pleural cavity was free from tumor. The heart weighed 300 gm. and its subepicardial fat was markedly reduced in amount. At the apex, questionably arising from the subepicardial fat, there was an elevated tumor nodule measuring 3 cm. in diameter which had invaded the myocardium. The right lung showed marked compression by tumor, but there was no definite tumor within the lung parenchyma. The left lung was normal. The other organs showed no gross evidence of tumor.

Microscopic Examination. The fat from the pleura, pericardium, mesentery, peritoneum, popliteal space and mediastinum showed numerous tumor nodules. The cells varied considerably in size and shape, had pale blue vesicular nuclei, and fine nucleoli. In many instances, the nuclei had been compressed to a crescentic outline by the large amounts of fat present. Other tumor cells showed oval, homogeneous nuclei with clear, pale cytoplasm and well defined cellular outlines. Sudan III stain showed large amounts of fat which was almost entirely cytoplasmic. Best's carmine stain for glycogen demonstrated large amounts of cytoplasmic glycogen within practically all tumor cells. In the cells where globules of fat had compressed the cytoplasm, this compressed area was stained positively for glycogen. The tumor in the liver was clearly demarcated, had an apparent connective tissue capsule, and was similar to tumor observed elsewhere. The tumor thought to represent lymph node replacement was shown to be merely nodules of tumor of the same size as lymph nodes. Connective tissue stroma was extremely variable, and numerous areas of necrosis were observed. Thrombosis of the small vessels was widespread.

COMMENT

This patient had numerous fatty, soft-tissue tumors arising in areas where fat is normally present. Tumor was found in the three most common sites: the popliteal spaces, buttocks and retroperitoneal spaces, as well as other and rarer locations. There was recurrence of tumor growth after excision in both the popliteal space and the thigh.

This type of liposarcoma grows rather slowly. There are numerous examples of solitary liposarcoma reported in the literature with short or no follow-up histories. It is possible that some of those patients may eventually develop other tumors.

There are four cases in the foreign literature which illustrate the occurrence of multiple primary fatty tumors. In 1925, Fahr and Lubarsch³ described a case entitled "A Metastasizing Lipoma" in which there were multiple tumors, apparently of fatty origin, present around the kidney, in the retroperitoneal region, in the mesentery, serosa, posterior mediastinum, the apex of the heart, the liver and the bone marrow. The authors thought that the original tumor arose from the fat around the kidney and metastasized to the other sites. Nienhuis,⁴ too, reported a case of multiple fatty tumors involving mesentery, retroperitoneal tissues, pancreas, extradural tissues and thoracic vertebrae. These tumors were of at least 2 years' duration and Nienhuis concluded that only the vertebral and extradural lesions were metastatic, the others representing primary malignant fatty tumors. He stated that the case reported by Fahr and Lubarsch presented the same picture, rather than a single primary liposarcoma with metastases. In 1934, Siegmund⁵ reported a beautiful example of multiple primary malignant fatty tumors occurring in a male of 65 in whom the first tumor was noted in the soft tissue of the thigh. At autopsy, there were numerous individual fatty tumors arising within the pleural cavity, omentum, mesentery, serosa of small and large intestine, along the aorta, surrounding both kidneys, in the soft tissues of the back, thigh and upper arms, the subepicardial fat, and in the bone marrow. He concluded that this was a systemic malignant disease of fatty tissue and should be designated as a "lipoblastische Sarkomatose." He emphasized that a parallelism might be drawn between this and other systemic diseases such as neurofibromatosis and lymphosarcoma. He also independently came to the conclusion that Fahr and Lubarsch's case represented multiple primary tumors. Goormaghtigh,⁶ in his extensive review of malignant fatty tumors in 1936, commented on Siegmund's case and reported an additional case of a 59-year-old woman whose first tumor was located in the left half of the abdomen. Radiotherapy was of no value. At autopsy, numerous individual malignant fatty tumors located in the soft tissue of the thigh, the base of the heart, in the gastrocolic, gastrosplenic and suspensory ligament of the liver, were found. There were numerous other tumors arising from the fat of the serosa of the small and large intestine, omentum and mesentery, making a total of 219 individual tumor masses. There was

no evidence of lymph node involvement. The bones, unfortunately, were not examined.

These four well documented cases and the case here reported represent multiple primary malignant fatty tumors and give further support to the conception that adipose tissue should be considered as a single organ subject to its own diseases.

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[Illustrations follow]

DESCRIPTION OF PLATES

PLATE 148

FIG. 1. Profile view of soft-tissue liposarcoma of the back.

FIG. 2. External surface of retroperitoneal tumor, showing lobulations.



Multiple Primary Liposarcomas

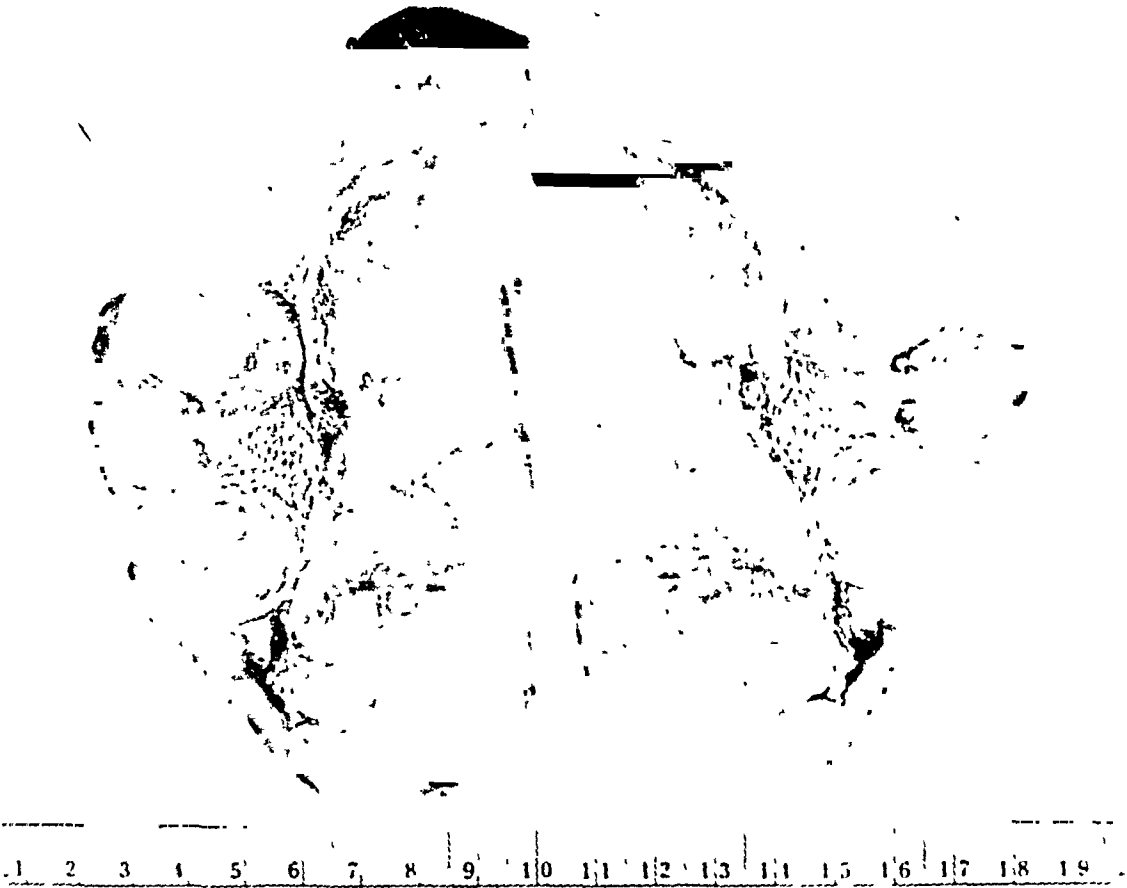
PLATE 149

FIG. 3. Cut section of retroperitoneal tumor.

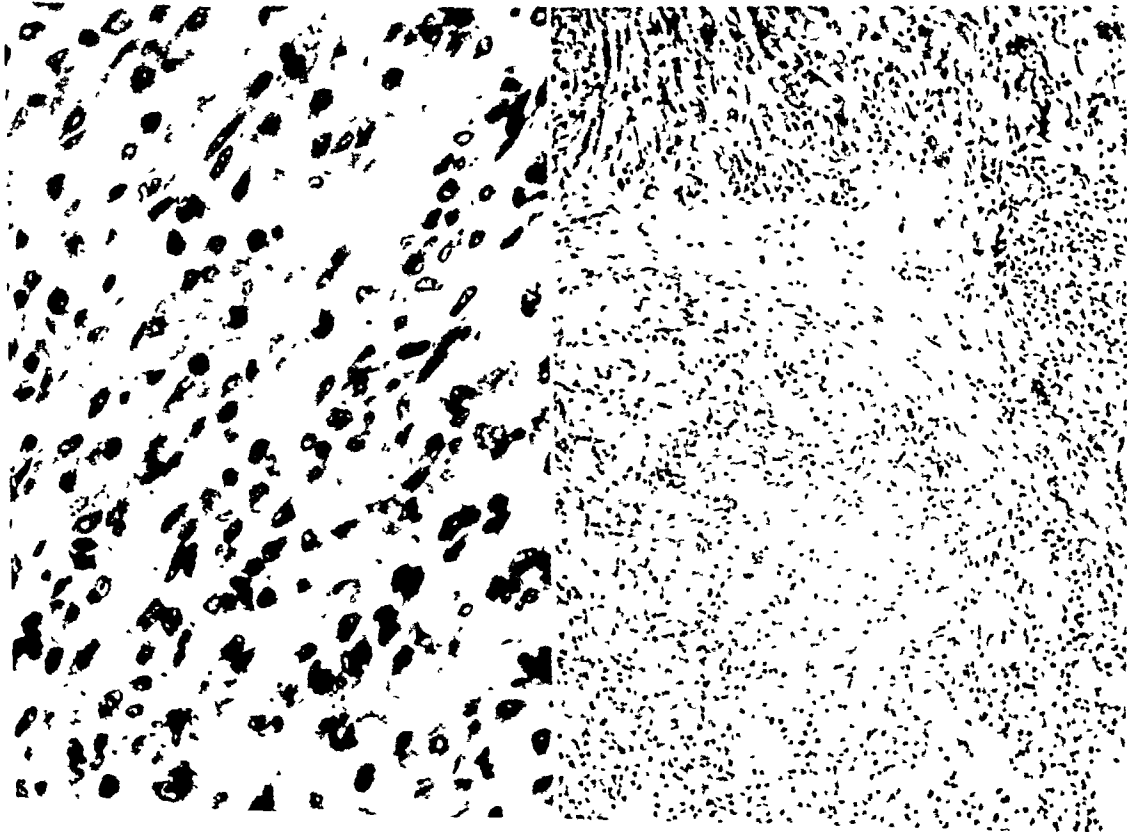
FIG. 4. Characteristic structure of one of the soft-tissue liposarcomas. $\times 303$.

FIG. 5. Tumor replacing liver parenchyma. $\times 97$.

3



4



5

Ackerman

Multiple Primary Liposarcomas

TRUE HERMAPHRODITISM

REPORT OF A CASE WITH MAMMARY CARCINOMA *

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Because of the psychologic and sociologic implications of hermaphroditism, as well as its obvious biologic significance, the problems raised by this condition merit thoughtful consideration. *True* hermaphroditism, as illustrated in the case herein presented, may be defined as the exceedingly rare condition in which both testis and ovary are found in the same individual, either separately or in combination as an ovotestis. According to a careful study by Young,¹ only 20 confirmed cases had been reported in the world's literature before 1937.

False hermaphroditism is a relatively common condition which may closely simulate the true type. The distinguishing feature of pseudohermaphroditism is the presence of gonads of only one sex, whatever combinations of accessory sex organs and anomalies of external genitalia may be present. Over 2,000 cases of false hermaphroditism have been described. Careful investigation is required to differentiate the two conditions, and the diagnosis of true hermaphroditism cannot be confirmed without either biopsy or autopsy studies. As Novak² pointed out, many patients with the "feminine type" of hermaphroditism are really females in whom a tumor of testicular type, such as an arrhenoblastoma, has developed in the ovarian substance. The resulting structure is, of course, entirely different from an ovotestis but may give rise to the same manifestations.

To the following case, none of these objections can apply. The pathologic studies are extensive and conclusive and are supported by the clinical data.

REPORT OF CASE

Clinical Findings. The patient was a former shoe-worker, married and 79 years of age. For the preceding 8 or 9 years he had shown gradual deterioration of personality and intellect, becoming querulous, irritable and confused. The patient had always been feminine in appearance and reactions, but at 26 years of age he had married a maternal type of woman, with whom he made an apparently satisfactory adjustment despite his total inability to perform coitus. Every month until middle life he "menstruated," with severe physical pain accompanying the process. Family history was irrelevant except for gastric cancer in the mother, cancer (unspecified) in one sibling, and psychosis (unspecified) in another sibling.

Physical examination upon admission disclosed little except for very small external genitalia of the male type, with no right testis palpable, and feminine secondary sex characteristics. The penis was only 1½ inches in length. The scrotum was

* Received for publication, October 4, 1943.

† Now in the Medical Corps, U. S. N.

well formed. There was no evidence of hypospadias, nor of any vaginal opening. Laboratory data were noncontributory.

In the hospital the patient was depressed, agitated and whining. He wandered about aimlessly and showed marked clouding of the sensorium and loss of intellectual resources. Three weeks after admission there developed thrombosis of a femoral vein, and subsequently he died of pulmonary embolism.

Psychiatric Diagnosis. Senile psychosis, depressed and agitated type.

Macroscopic Findings

The pertinent findings have been abstracted from the report of the autopsy.

Pelvic Organs. The bladder was of normal size and appearance. However, on the posterior surface there was a firm ridge, running diagonally from the left side of the base of the bladder upward and to the right. This was about 12 cm. long and varied from 1½ to 2 cm. in diameter. On section through this, numerous small cystic cavities were seen, located approximately in the center of firm muscular tissue, which formed the bulk of this ridge. This represented an anomalous and distorted uterus. From the apex of this organ there extended a small, thin, cord-like structure which passed over the pelvic brim and terminated near a firm, white, wrinkled structure measuring 2 by 1½ by ½ cm. The latter resembled in every respect a senile ovary, both externally and on section.

In the left half of the scrotum there was a small, firm, fibrous, brownish red testis, with a fair-sized but atrophic-appearing epididymis. The spermatic cord on that side was quite well developed, and the vas deferens could be identified. In the right side of the scrotum no evidence of testis or epididymis was found. The prostate was in its usual location at the neck of the bladder. It was of approximately normal size and consistency and on section appeared normal.

Breasts. Both breasts were enlarged but not pendulous. The nipples were small and of the male type. The left breast contained a firm white mass (4 by 4 by 2 cm.), which was fairly circumscribed but whose edges were not sharply defined. The tissue had the appearance of a carcinoma. The glandular tissue of both breasts had considerable fatty tissue incorporated in it, but itself appeared abundant.

Brain. The brain was slightly smaller than normal. The arteries at the base showed only moderate arteriosclerosis. The ventricles were somewhat enlarged because of the cerebral atrophy. The pituitary body appeared slightly larger than usual but was otherwise normal.

Gross Pathologic Diagnoses. Pulmonary embolism with infarction; moderate cerebral arteriosclerosis, with minimal generalized arteriosclerosis; cardiac dilatation; true hermaphroditism, with the presence of a prostate, one testis, one ovary and a uterus; feminine type of

secondary sex characteristics and enlarged breasts; cerebral atrophy (senile?); carcinoma of left breast.

Microscopic Findings

Ovotestis. The sections of ovotestis showed two distinct types of tissue arrangement. Approximately one-third of the area consisted of densely packed, elongated nuclei in a dense network of hyaline fibers surrounding typical corpora albicantia (Figs. 1 and 2). The other part of the section was composed of finely fibrillar, scantily nucleated, fibrous tissue; this contained clumps of large cells with spherical and oval nuclei and clearly demarcated, abundant eosinophilic cytoplasm (Figs. 3 and 4). The structure of these clumps was identical with that of the islets seen in the atrophied testicle in the scrotum. Adjacent to the border of this portion of the section were irregular tubular structures lined by low-columnar, nonciliated epithelium.

Testis. Tubular structures of the testis were simulated by finely reticular connective tissue, packed together in areas defined by compact, densely staining, sparsely scattered connective tissue nuclei. The areas thus outlined were of the size and shape of atrophied testicular tubules. In addition there were clumps of large cells with spherical and oval nuclei and with eosinophilic, clearly demarcated cytoplasm (Figs. 5 and 6).

Prostate. The prostate showed irregular glands with tall columnar epithelium in a fibromuscular stroma. Many glands contained corpora amylacea.

Uterus. The section of uterus appeared as the cross section of a tube with smooth muscle and little connective tissue. The lumen was lined by columnar cells, in places arranged as tubular glands surrounded by stromal cells, like those of atrophied endometrium.

Breast. There were fibrous bands in the breast containing ducts, singly and in groups, with abundant fat between the bands. Another section showed acini adjacent to ducts. Some of the acini contained homogenous eosinophilic material.

Breast Nodule. The breast nodule consisted of strands and nests of anaplastic epithelial cells, some forming atypical glandular structures invading atrophied breast tissue (Figs. 7 and 8).

Pituitary Gland. The varying types of cells were distributed in normal proportion and all lobes appeared normal.

Microscopic Pathologic Diagnoses. Atrophied testicle and epididymis; atrophied ovotestis; atrophied uterus; adenocarcinoma of breast; female type of atrophied breast (gynecomastia); infarcts of lung; embolism of pulmonary artery; bronchopneumonia; infarcts of kidney; lipid lymphocytosis of spleen (type not determined).

Tabulation of Clinicopathologic Features
(as Suggested by Young¹)

1. Source of materialautopsy
2. Age 79
3. Reared asmale
4. Emotionsmale(?)
5. Bodily aspectsmale external genitalia; feminine
secondary sex characteristics
6. Mensesfrom puberty to middle life
7. Phallusnot hypospadiac
8. Vaginal openingnone
9. Uterus locatedalong posterior surface of bladder
10. Right gonadtrue ovotestis
11. Left gonadtestis in scrotum

COMMENT

Although this patient's deficiencies were hazily appreciated early in life, he led outwardly a fairly conventional male existence. In contrast to some hermaphrodites, who boast of their sexual capabilities, he passively accepted his situation. Libido remained at an infantile level; potency was nil. From a psychosomatic standpoint, it is very interesting to note that when he succumbed to the senium, his psychosis took the form of the depressed and agitated type, indicating his fundamental sense of insecurity.

A noteworthy finding was the carcinoma of the breast. The possible endocrine factors underlying this development constitute a stimulating subject for speculation.

In the earlier investigation of hermaphroditism, the anatomic aberrations were described in great detail, with little or no attention being paid to physiologic and psychologic features. More recently, with the stressing of the functional aspects, the endocrine side of the picture has been illuminated. It is now well known that the urine of even a normal person contains hormones of both sexes. Thus in the urine of a normal male the ratio of excretion is usually about 5 androgenic units to 1 estrogenic unit, and vice versa in a female. It is not surprising, therefore, to find in the psychologic make-up of every man some feminine characteristics. In other words, the difference between man and woman is in many ways more apparent than real. When viewed in this light, a problem such as homosexuality becomes more understandable. Recent endocrine studies tend to support the hypothesis that there is a disturbance in the balance of sex hormones in this condition. For instance, Glass, Deuel and Wright³ found that sex

hormone assays in a group of male homosexuals yielded androgen:estrogen ratios which appeared to be significantly lower than those obtained in a group of normal males. Thus the majority of patients labeled "homosexual" might more properly be described as "bisexual" and may be regarded as "psychologic hermaphrodites."

Although it is beyond the scope of this paper to discuss the treatment of hermaphroditism, it might be well to mention that in younger patients the outlook is frequently far from hopeless. For instance, Doss and Priestley⁴ described good results in a 12-year-old child, treated by surgical removal of all female tissues, preservation of all male tissues, and postoperative administration of testosterone. Here, again, success was furthered by treatment of the total individual rather than of an anatomic condition. Psychosomatic features and endocrine interrelationships must be carefully considered.

SUMMARY

In an aged patient with senile psychosis, true hermaphroditism was confirmed by the demonstration of a right ovotestis and left scrotal testis. Secondary sexual characteristics were of feminine type. In the left breast there was a primary adenocarcinoma. The occurrence of this neoplasm invites attention to the endocrine features of hermaphroditism, which, together with the psychologic aspects, far outweigh the anatomic state in importance. Practical application of the data obtained from the study of hermaphroditism may be utilized in promoting a better understanding of such widespread clinical problems as that of homosexuality.

I wish to express my appreciation to Dr. David Dial (deceased) of the New Hampshire State Hospital and to Dr. R. E. Miller of Dartmouth Medical School for the pathologic reports; and to Dr. W. W. Greulich of Western Reserve University Medical School for the photomicrographs.

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[Illustrations follow]

DESCRIPTION OF PLATES

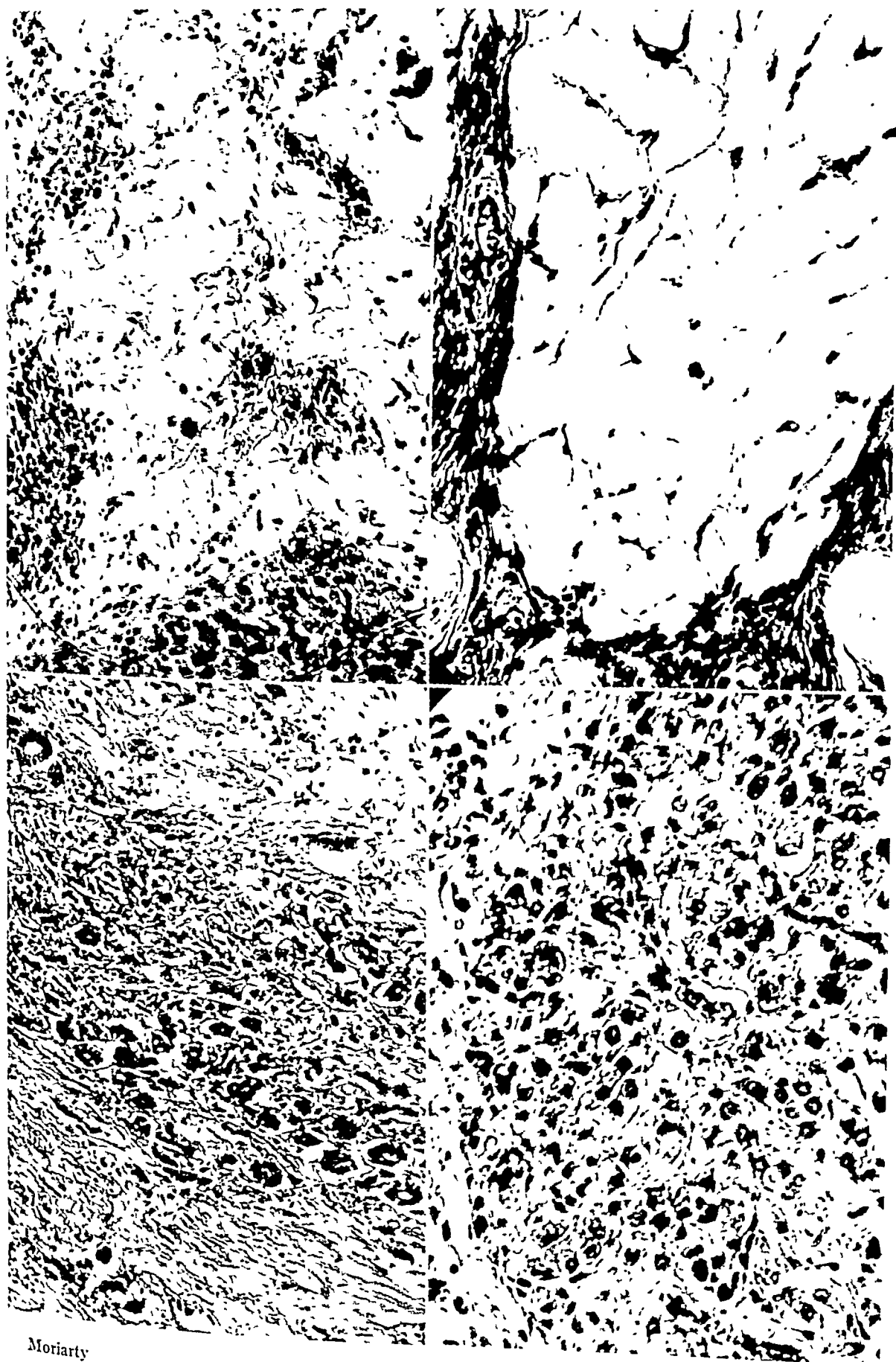
PLATE 150

FIG. 1. Section of ovotestis, showing corpora albicantia. $\times 129$.

FIG. 2. Section of ovotestis, showing corpus albicans. $\times 247$.

FIG. 3. Section of ovotestis, showing clumps of interstitial cells. $\times 129$.

FIG. 4. Section of ovotestis, showing clump of cells of testicular type. $\times 247$.



Moriarty

True Hermaphroditism

THE EFFECTS OF 3,4 BENZPYRENE ON WOUND REPAIR IN THE SKIN OF MICE *

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The regenerative power of the epidermis differs in various species and, under the same experimental conditions, depends upon the number of cells present in the original epithelial layer.¹ In the rat and pigeon, a skin defect heals more slowly than a defect of equal size in the guinea-pig.² The epidermis of the guinea-pig has, in a given area, more cells than the skin of the rat and pigeon. The more numerous the epidermal cells, the greater is the speed with which skin defects are repaired.²⁻⁴

Accordingly, it might be assumed that within the same species, hyperplastic skin may show greater regenerative power than normal skin. Since an early effect of carcinogenic hydrocarbons on the skin is hyperplasia of the epithelium, a study of the regenerative processes taking place in skin thus rendered hyperplastic was thought a suitable test of this assumption. It might at the same time give some further insight into the mode of action of these carcinogenic substances on the epithelial cells.

MATERIAL AND METHODS

Sixty-six male and female mice of the closely inbred strains, C57 black and leaden, 6 to 8 weeks old, were used. The animals were kept on a diet of Purina Chow and water, both being available at all times.

The mice were divided into three groups. The experimental group consisted of 33 animals receiving applications of 0.3 per cent 3,4 benzpyrene dissolved in benzene. The hair over the lower back was carefully clipped without injury to the underlying skin; 8 drops of the benzpyrene solution were applied at each treatment by means of a dropper. The treatment was repeated three times weekly for periods of 2 weeks and 1, 2 and 3 months, respectively. After each of these periods, a circular piece of skin and subcutaneous tissue, measuring 3 mm. in diameter, was excised from the painted area with a pair of curved scissors. Regeneration was allowed to take place for 3, 5, 8 and 10 days.

Two groups of animals served as controls: one, of 17 mice, was treated with the solvent benzene alone; the second control group, con-

* This investigation was made possible through a grant of Mr. M. J. Bernstein, establishing a Fellowship for research in cancer in memory of his son, Dr. Albion O. Bernstein.
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sisting of 16 animals, was untreated. In both control groups, excisions were made similar to those in the benzpyrene group, and equal periods of time were allowed for regeneration.

In 16 of the mice receiving benzpyrene dissolved in benzene and in all of the animals receiving benzene alone, a second piece of skin was removed from an untreated area of the skin as additional control material.

At the end of the experimental periods, the animals were killed with chloroform. In view of the diurnal mitotic rhythm present in the skin of mice,⁵⁻⁷ the animals were sacrificed at the same time of the day, namely, between 10 A.M. and 12 noon. A piece of epidermis comprising the area of the excision, together with the adjoining skin, was removed, stretched on filter paper, fixed in 8 per cent solution of Formalin (3.2 per cent formaldehyde), embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

The changes taking place (1) in the marginal epithelium surrounding the defect, and (2) in the new epithelium that grows out from the periphery towards the center of the wound will be described separately. The outgrowing epithelium formed a tongue with a broad insertion and a more or less pointed tip.

The number of rows of cells in the marginal as well as in the regenerating epithelium was determined. In the outgrowing epithelial tongue, the cell rows at its insertion and in the advancing tip were counted separately. The length of the advancing tip was measured with an object micrometer. Our method follows closely that used by Loeb and his co-workers¹⁻⁴ in their studies on wound repair.

Mitoses were counted in each of the areas specified. Since mitoses are much more frequent in the hair follicles than in the rest of the skin, only mitoses in the epidermis between the hair follicles were counted. The number of mitoses under the various experimental conditions is given in multiples of the normal. This seemed preferable to giving absolute figures because it allows for the variations existing in various areas.

OBSERVATIONS

A. IN NORMAL MICE

At all stages throughout the 10 days of observation subsequent to excision, the wound was covered with a scab that steadily decreased in size.

Histological Examination

(1) *Marginal Epithelium.* The epidermis consisted of 2 rows of cells. The upper layer was composed of flat, slightly keratinizing elongated spinous cells; the deeper layer consisted of cuboidal basal cells. The ratio between basal and spinous cells was 2:1 to 3:1.

Mitoses were found only in the basal cells at the ratio of 1:850 basal cells, or 1:1200 epithelial cells including the spinous cells.

At 3 and 5 days following excision, the epithelial layer was thickened and markedly keratinized. The basal cells were 30 to 50 per cent larger than usual; they assumed a cylindrical shape and were oriented in a direction perpendicular to the surface. Their nuclei stained more lightly with hematoxylin than ordinarily; the chromatin had the shape of thin, elongated threads, and the nucleoli had disappeared. These changes were most accentuated in areas close to the margin of the wound. Mitotic proliferation of the basal cells was increased and reached a maximum of from four to six times the normal rate.

Eight and 10 days after operation, there was a gradual return to the resting stage. The cells again became smaller, the nuclei stained more deeply with hematoxylin, and the nucleoli were more definite. The number of mitoses had declined, but was still two or three times greater than usual.

(2) *New Epithelium*. Hypertrophic epidermal cells grew out from the margin of the wound in a tongue-like manner under the blood clot that covered the defect of the skin. At its insertion, this tongue consisted of at least 3, but more frequently of 4 or 5 rows of hypertrophic cells. At its tip, the tongue was thinned out and was composed of 1 to 3 rows of cells. The farther the cells had advanced into the wound, the more they were stretched out.

Mitotic proliferation was at from four to six times the normal rate at its peak, which was found 5 and 8 days after excision. The movement of the cells was most active during the first 5 days. At later stages, cell migration was slowed down. In one of four examples, the defect began to close 10 days after operation. Details of these changes are given in Table I.

B. IN MICE TREATED WITH BENZENE

The skin underwent thickening and increased keratinization. After 2 to 3 months of treatment, there was some loss of hair in some animals. As compared with the untreated mice, wound repair was hastened. Eight days after operation, the wounds were covered with a small crust. After 10 days, the site of excision was difficult to recognize, whereas in the untreated animals there was still a small defect covered with a scab at this stage.

Histological Examination

(a) Treatment for 2 Weeks and (b) for 1 Month

(1) *Marginal Epithelium*. The epidermis consisted of 2 or 3 rows of cells instead of 2 as in untreated mice. In the latter, pieces of skin

350 μ long contained from 58 to 68 cells (Table IV, column 4), the ratio between basal and spinous cells being 2:1 to 3:1 (Table IV, column 6). In the benzene-treated animals, on the other hand, pieces of epidermis of the same length contained 78 and 86 cells respectively, and the ratio of basal and spinous cells had shifted in favor of the spinous cells (1:1 and 1.3:1 instead of 2:1 to 3:1). There was increased keratinization in the hair follicles and in the surface epithelium at some distance from the wound. Scattered polymorphonuclear and mononuclear leukocytes were seen in the subcutis. During the first 5 days fol-

TABLE I
Normal Animals

Days after excision	No. of animal	No. of rows of cells in			Length of tongue (mm.)	No. of mitoses in multiples of the normal	
		Marginal epithelium	Insertion of tongue	Tip of tongue		Marginal epithelium	New epithelium
3	40	2	3-4	2	0.28	2-3	0
	68	2	2-3	1-2	0.18	2-3	0
	67	2	4-5	2-3	0.31	4-6	2-3
	49	2	3-4	2	0.29	4-6	2-3
5	35	2	4-5	2-3	0.38	4-6	4-6
	73	2	4-5	3	0.42	4-6	4-6
	12	2	4-5	2-3	0.33	4-6	4-6
	48	2	5	3	0.46	4-6	4-6
8	22	2	4-5	2-3	0.52	2-3	4-6
	69	2	4-5	2-3	0.62	2-3	4-6
	47	2	4	1-2	0.58	2-3	4-6
	46	2	5	3	0.67	2-3	4-6
10	31	2	4-5	3	0.72	2-3	2-3
	74	2	4	2-3	0.69	2-3	2-3
	45	2	4-5	2-3	0.78	2-3	2-3
	27	2	4-5	3	Closing	2-3	2-3

lowing excision, the epithelial cells were about 50 per cent larger than ordinarily, and had undergone marked proliferation. Mitotic division began sooner after operation and was more intensified than in untreated controls (Table II). Whereas in the latter, mitoses had increased four to six times at 5 days after excision, in the benzene-treated mice the corresponding values were six to nine times the normal. Eight and 10 days after operation, the number of mitoses had declined and had, in some instances, returned to normal in contrast to the untreated mice in which the number of mitoses dropped more slowly.

(2) *New Epithelium.* At its insertion, the tongue revealed 4 to 8 rows of cells (3 to 5 in untreated mice). The maximum thickness was reached 5 days after excision. The cells grew out more rapidly towards the center of the wound than in the untreated animals. In the latter, 3 days after operation, the tongue was 0.27 mm. long (maximum, 0.31

mm.; minimum, 0.18 mm.); in the benzene-treated animals, 0.33 mm. (maximum, 0.35 mm.; minimum, 0.31 mm.). After 5 days, the corresponding figures were, for the untreated animals, 0.40 mm. (maximum, 0.46 mm.; minimum, 0.33 mm.); for the benzene-treated mice, 0.57 mm. (maximum, 0.60 mm.; minimum, 0.53 mm.). After 8 days, the tongue was 0.60 mm. (maximum, 0.67 mm.; minimum, 0.52 mm.) long in the untreated animals; in the two benzene-treated mice, the tips of the tongues advancing from both sides of the excision had met, indicating the beginning closure of the defect, whereas only in one of

TABLE II
Animals Treated with Benzene

Duration of treatment	No. of days after excision	No. of animal	No. of rows of cells in			Length of tongue (mm.)	No. of mitoses in multiples of the normal	
			Marginal epithelium	Insertion of tongue	Tip of tongue		Marginal epithelium	New epithelium
2 weeks	3	41	3	5	3	0.35	4-6	4-6
	5	36	2-3	6-7	3-4	0.53	6-9	4-6
	8	39	2	5-6	2	Closing	2-3	2-3
	10	32	1-2	6	2-3	Closing	1	2-3
1 month	3	75	2-3	4-5	2-3	0.31	4-6	2-3
	5	51	2-3	7-8	3-4	0.60	6-9	6-9
	8	76	2-3	5-6	2-3	Closing	1	4-6
	10	65	2	6-7	3	Closing	2-3	2-3
2 months	3	4	2-3	4	2-3	0.29	2-3	2-3
	5	13	2-3	7-8	3-4	0.61	6-9	6-9
	8	59	3	6	2-3	Closing	1	2-3
	10	23	2-3	7-8	3	Closing	2-3	2-3
3 months	3	52	3	5-6	3-4	0.38	4-6	4-6
	5	53	3	9	4	0.69	6-9	6-9
	8	3	3	6-7	3-4	Closing	2-3	2-3
	8	5	2-3	4-5	2-3	0.62	2-3	4-6
	10	28	2-3	7	3	Closing	1	2-3

the four untreated mice had the wound begun to close 10 days after operation (Tables I and II).

The tip of the tongue consisted of 2 or 3 rows of cells after 3 days, and of 3 or 4 rows 5 days after operation; in the later stages of regeneration there was a slight decrease in the thickness of the tongue of cells.

The mitotic count was increased over that seen in untreated controls and reached its peak (six to nine times the normal) 5 days after excision (Table II); after 8 and 10 days, when the wounds began to close, the number of mitoses dropped sharply.

(c) Treatment for 2 and (d) for 3 Months

(1) *Marginal Epithelium.* After 2 and 3 months there was no further intensification of the growth processes nor of keratinization as compared with conditions seen after 1 month of treatment. However,

some degenerated epithelial cells and cell débris were now found in the cutis. Moreover, the hypertrophy of the regenerating epithelium receded more slowly than in the mice treated for 1 month only. Ten days after operation, the cells had not returned to the resting state.

(2) *New Epithelium*. The outgrowing tongue was somewhat thicker at its insertion (4 to 9 rows of cells) than in the animals treated for 1 month (4 to 8 rows of cells); neither was there much difference in the length and thickness of the outgrowing tongue of cells (Table II).

C. IN MICE TREATED WITH BENZPYRENE

After application of benzpyrene for 2 weeks, depilation of the skin was accentuated in most animals. The epidermis was rough and brittle, markedly thickened and covered with a thick layer of keratin. These changes increased under prolonged treatment. Of the 33 mice, 4 had papillomas; in 1 of these a carcinoma had developed. In 1 animal a carcinoma was seen without previous appearance of papillomas. Details are given in Table III.

As was the case in the benzene-treated mice, wound repair was hastened after 2 weeks and, in some instances, after 1 month of application of benzpyrene. After 2 and 3 months of treatment with benzpyrene, however, the closure of the wound was, at all stages of regeneration, delayed, and as late as 10 days subsequent to operation the wound defects were still large.

Histological Examination

(a) Treatment for 2 Weeks

(1) *Marginal Epithelium*. The cytoplasm and the nuclei of the basal cells were larger than after treatment with benzene for a corresponding period. Three days after operation the number of mitoses was increased four to six fold; after 5 days it had reached six to nine times its normal value; after 8 and 10 days, as the wound began to close, mitoses decreased slightly, but their number was still higher than in either untreated or benzene-treated mice of the corresponding stages (Tables I to III). Farther away from the excision, the ratio of basal and spinous cells was 1.3:1 and 1:1 respectively, as had been the case in the benzene-treated animals (Table IV). The epidermis consisted here of 2 to 5 rows of cells as compared with 1 to 3 in the benzene-treated mice. Mitoses had increased to four to nine times the normal number. However, some basal cells exhibited karyorrhexis, karyolysis, or pyknosis. The spinous cells had undergone marked keratinization. The lumina of the enlarged hair follicles were filled with considerable amounts of keratin. Here and there, polymorphonuclear

and mononuclear leukocytes were seen. These changes varied in intensity in different animals.

(2) *New Epithelium*. The size of the cells and the number of rows

TABLE III
Animals Treated with Benzpyrene

Duration of treatment	No. of days after excision	No. of animal	No. of rows of cells in			Length of tongue (mm.)	No. of mitoses in multiples of the normal	
			Marginal epithelium	Insertion of tongue	Tip of tongue		Marginal epithelium	New epithelium
2 weeks	3	42	2-3	6-7	3-4	0.39	4-6	4-6
	3	43	3-4	7	4-5	0.44	4-6	4-6
	5	37	2-3	6-7	4-5	0.61	6-9	6-9
	5	38	3-4	8	6-7	0.68	6-9	6-9
	8	24	4	8	2-3	Closing	4-6	6-9
	8	26	3-4	8-9	3	Closing	4-6	4-6
	10	33	3-4	7	2-3	Closing	2-3	4-6
	10	34	3	8	3	Closing	4-6	6-9
1 month	3	77	2-3	5	4	0.29	2-3	2-3
	3	78*	4	6	4	0.28	2-3	2-3
	5	9†	2-3	5	1	0.36	4-6	4-6
	5	50	1-2	6	3	0.54	6-9	6-9
	8	79	2-3	5-6	3	Closing	4-6	4-6
	8	80	2-3	7-8	3	Closing	6-9	6-9
	10	72	3-4	7-8	3-4	Closing	4-6	6-9
	10	81	2-3	5	2	Closing	4-6	4-6
2 months	3	11	4-5	6	6	0.12	6-9	4-6
	3	71	3-4	5	6-7	0.08	6-9	4-6
	5	14	2-3	5	1-2	0.22	6-9	4-6
	5	62	2-3	4-5	1	0.28	10+	6-9
	8	70	2-3	7-8	3	0.26	4-6	6-9
	8	63	3	10-11	2-3	0.31	6-9	10-
	10	25‡	3	11-12	2-3	0.34	6-9	10-
	10	64	2	6-7	1-2	0.28	4-6	10-
3 months	3	66		8	1-2	0.09	6-9	4-6
	3	56		7	2	0.11	10+	6-9
	5	60§		11-12	1	0.17	10+	10+
	5	57¶		9-10	1-2	0.21	10+	10+
	8	61		12	2-3	0.22	10+	10+
	8	58		10-11	2	0.18	6-9	10+
	8	6		11-12	1-2	0.33	6-9	10+
	10	29		9-10	1-2	0.29	10+	10+
	10	30		10-11	1-2	0.36	6-9	10+

* Sick, pneumonia found at necropsy.

† Papilloma noted after 50 days.

‡ Papilloma noted after 45 days.

§ Papilloma noted after 52 days.

¶ Papilloma noted after 30 days, changed gradually into carcinoma.

|| Carcinoma noted after 90 days.

of cells at the insertion of the tongue of cells paralleled the condition in the marginal epithelium. Three days following operation, the cells were much enlarged and the number of cell rows was increased to 6 or 7. The frequency of mitoses was four to six times as great as in normal skin. After 5 and 8 days, the number of rows of cells was 6 to 9; the

mitotic count had further increased. Likewise after 10 days, the number of mitoses remained elevated.

After 3 days, the tip of the tongue of cells was thicker (3 to 5 rows of cells) than in the untreated animals (1 to 3 rows) or in the benzene-treated group (3 rows). The regenerating cells were enlarged and there was intense mitotic proliferation. The nuclei stained lightly with hematoxylin; the chromatin network was fine and delicate. The tips of the tongues of cells measured 0.44 and 0.39 mm. in length, as compared with 0.35 mm. in the benzene-treated and 0.27 mm. in the un-

TABLE IV

Total Number of Cells, Number of Mitoses in 10,000 Basal Cells and Ratio of Basal to Spinous Cells in a Field of the Marginal Epithelium of the Skin, Measuring 350 μ in Length, 3 Days after Excision

		No. of mouse	Total no. of cells	No. of mitoses in 10,000 basal cells	[Ratio] basal: spinous cells
Normal		40	60	31	2:1
		68	58	27	2:1
		67	68	52	3:1
		49	62	49	2:1
Benzene applied for:	2 weeks	41	78	51	1.3:1
	1 month	75	86	54	1:1
	2 months	4	94	55	1:1
	3 months	52	85	52	1:1
Benzpyrene applied for:	2 weeks	42	70	44	1.3:1
	2 weeks	43	82	51	1:1
	1 month	77	78	53	1:1.2
	1 month	78	86	55	1:1.3
	2 months	11	120	52	2:1
	2 months	71	84	75	1:1
	3 months	66	130	56	2:1
	3 months	56	125	94	2.7:1

treated animals. After 5 days, 4 to 7 rows of cells were counted instead of 2 to 4 as in the benzene-treated and control groups. The cells remained enlarged and mitoses were frequent. The tongues had grown out still further and measured 0.68 and 0.61 mm. respectively as compared with 0.53 mm. in the benzene-treated and 0.40 mm. in the untreated mice. After 8 and 10 days, the wound began to close in all four animals. The cells were still hypertrophic, and mitotic proliferation was elevated over that in both the benzene-treated and control groups (Tables I to III).

(b) Treatment for 1 Month

(1) *Marginal Epithelium.* Hypertrophic and degenerating cells were frequently found. Three and 5 days after excision, the mitotic activity appeared to be less in three of four instances as compared with the

corresponding stages of wound healing after 2 weeks of treatment. Eight and 10 days after operation, the number of mitoses was the same as after 2 weeks of treatment in two cases. In the other two instances, the mitoses were increased as compared with those found after 2 weeks of treatment. However, the ratio between basal and spinous cells had now changed to 1:1.2 and 1:1.3 respectively (Table IV). Thus, the decrease of mitoses was only relative to the total number of cells, and was not true in proportion to the number of basal cells (Table IV), in which alone mitoses occurred. At some distance from the margin of the wound, the basal cells had not further increased in size as compared with the 2 weeks' stage. Their nuclei had become irregular and were shrunken and condensed. The regressive changes and also keratinization were intensified. The number of cells in a field 350 μ long was the same as after 2 weeks of treatment. The number of rows of cells was 1 to 4; mitoses were now two or three times as frequent as in the normal epidermis (Table III).

(2) *New Epithelium*. Three days after excision, the tongue at its insertion consisted of 5 or 6 rows of cells. The number of mitoses was two or three times the normal figure. After 5 and 8 days, the mitoses had increased still further (Table III). After 10 days, the cells had decreased in size, but the number of mitoses remained high (Table III).

After 3 days, the tip of the tongue was composed of 4 rows of cells, and the degree of hypertrophy of the cells was similar to that seen after 2 weeks of treatment with benzpyrene. The mitotic count was comparable to the corresponding experiments in the benzene-treated group (Tables II and III). Some nuclei were pyknotic, and the lengths of the tongues were 0.29 and 0.28 mm. as compared with 0.31 mm. in the benzene-treated group and 0.27 mm. in the untreated animals. After 5 days, mitotic proliferation and outgrowth had made progress. The tongues were now 0.36 and 0.54 mm. long as compared with 0.60 mm. in the benzene-treated and 0.40 mm. in the untreated mice. After 8 and 10 days, mitotic proliferation was increased over the values found in the benzene-treated group, and the wound had begun to close in all four cases (Table III).

(c) Treatment for 2 Months

(1) *Marginal Epithelium*. The mitoses had increased to six to ten times the normal number during the early stages subsequent to excision, and they remained elevated (four to nine times) after 8 and 10 days. Farther away from the wound, the epidermis consisted of 2 to 5 rows of cells; the mitoses here were six to ten times as numerous as ordinarily. Some cells were now twice as large as usual. This increase of size of the

cells resulted in an increase in the thickness of the epithelial layer. Regressive changes and keratinization were even more accentuated than after 1 month of treatment. The cells were closely packed, and there were 100 in a field $350\ \mu$ long. The ratio of basal and spinous cells was 2:1 and 1:1 respectively (Table IV).

(2) *New Epithelium*. The number of rows of cells increased the longer regeneration was allowed to take place. Eight and 10 days after excision, as many as 12 could be counted. The epithelial layer consisted of large basal cells, small cuboidal cells in the midportion and flat keratinizing cells at the surface. The mitoses had increased to more than ten times the normal number, and the increase was the more pronounced the longer the interval after operation. After 3 days, the tips of the tongue of cells were very short, measuring only 0.12 and 0.08 mm. in length, as compared with 0.29 mm. in the benzene-treated and 0.27 mm. in the untreated groups (Tables I to III). While mitotic proliferation was intensified, the newly formed cells, instead of growing out into the wound, piled up on top of one another. Thus, there were 6 or 7 rows of small cells showing downgrowth rather than migration into the defect. Frequently, these cells showed karyorrhexis and pyknosis. After 5 days, the growth of the tongues in length had made slight progress; they had increased to 0.28 and 0.22 mm. respectively, instead of 0.61 mm. in the benzene-treated and 0.40 mm. in the untreated mice. The tongue was very thin and consisted of 1 to 3 rows of cells only. After 8 and 10 days, the outgrowth of the tongue had made very slight progress (Table III). Mitoses as well as degenerative changes in the cells were common. The downgrowth of the cells was accentuated, whereas the lengthwise outgrowth of the cells was inhibited or markedly delayed.

(d) Treatment for 3 Months

(1) *Marginal Epithelium*. The upward trend of mitotic proliferation that had been observed after 2 months of treatment continued throughout the periods of wound repair. Hyperplasia and hypertrophy of the epithelial cells were marked at some distance from the excision. The epidermis consisted of 3 to 5 rows of cells. In one field $350\ \mu$ long, as many as 130 cells were packed together. The ratio of basal and spinous cells shifted in favor of the basal cells (2:1 and 2.7:1; Table IV), due presumably to the mitotic activity which had increased ten times and more above the normal values (Table III).

(2) *New Epithelium*. Three days after operation, 7 or 8 rows of cells were counted, and after 5, 8 and 10 days, there were 9 to 12. There was, therefore, a notable multiplication of cells, and again the

increase in mitoses became more marked as the interval following excision increased. Large basal and small polyhedral cells took part in the proliferation. However, degenerative changes were common in these cells, and the cells continued to grow downward into the subcutis, whereas their outgrowth into the wound defect was markedly inhibited.

During all stages of wound repair, the outgrowth of the tongue was inhibited to a greater degree than after 2 months of treatment. The tip consisted of 1 to 3 rows of cells only; and while mitotic proliferation was more pronounced than after shorter treatment, karyorrhexis, karyolysis and pyknosis were frequently found. After 3 days, the tongues were 0.11 and 0.09 mm. long, and 10 days after operation had reached only 0.36 and 0.29 mm. respectively. The downgrowth of the small proliferating cells was even more accentuated than it had been after treatment with benzpyrene for 2 months. In this connection it is interesting to note that polymorphonuclear and mononuclear leukocytes had infiltrated the underlying connective tissue and the epidermis, although the intensity of this infiltration varied.

COMMENT

An analysis of the processes of repair in the skin of normal mice revealed certain relations between the growth processes in the original epithelium and in the new epithelium growing out into the wound defect. The original epithelium reacted to the making of the wound by hypertrophy and hyperplasia that reached a peak after 5 days. The cell migration into the wound was most marked during the first 3 days, whereas the proliferation of the new epithelium had its maximum after 5 and 8 days. Closure of the wound began at the earliest after 10 days and was associated with a decline of the growth processes.

Under the influence of benzene applied previous to excision, wound healing was accelerated with an intensification of both migration and growth of the epidermal cells. These processes reached their peak after 1 month of treatment, after which the rate of wound repair remained fairly constant at this elevated level.

Under the influence of benzpyrene, the course of wound healing depended in some respects on the duration of the treatment given previous to excision. After 2 weeks of application of benzpyrene, wound repair was accelerated over the normal to about the same degree as in the corresponding benzene-treated mice. However, the mitotic count did not recede as rapidly in the benzpyrene-treated mice as it did in the animals treated with benzene. After 1 month of treatment, epithelial regeneration was stimulated less than after 2 weeks of treatment. After 2 and,

still more so, after 3 months of application of benzpyrene, there was a definite inhibition or retardation of epithelial migration into the wound, as compared with the normal, while epithelial proliferation on the contrary was still further increased. This intensified mitotic proliferation at the margin of the wound caused both a piling up of the cells and a downgrowth into the underlying tissue.

The repair in the skin of normal mice resembles that described by Loeb and his co-workers¹⁻⁴ in rats, pigeons and guinea-pigs. There is a cycle of cellular proliferation and mitotic activity, and the process of healing is most active at a time when the wound is largest.

Benzene accelerates the growth processes and the curve of wound repair and does it increasingly, until a certain maximum has been reached beyond which there is no further stimulation. Such a maximum is seen not only at the site of wound healing itself, but also in the skin at a distance from the area of excision.

A growth-stimulating effect of benzene on the epidermis has recently been reported also by Rous,⁸ who observed the formation of papillomas in rabbits painted with benzene for long periods of time.

After 2 weeks and 1 month of application of benzpyrene, the proliferation of the epidermal cells and their movement into the wound defect were stimulated. This stimulation was similar to that seen after treatment with benzene alone; it might, therefore, be attributable partly to the action of the benzene used as a solvent for the benzpyrene. But if the excisions were made after 2 and 3 months of application of benzpyrene, the migration of the cells was inhibited, whereas their proliferation was further increased.

As to the cause of these changes in the reaction of the epidermal cells, the prolonged application of the carcinogenic agent may have resulted in injury to the epithelial cells that becomes manifest as a loss of motility. The occurrence of leukocytes may indicate such a toxic action of benzpyrene. In addition, changes in the base of the wound might interfere with cell migration. Since this form of movement represents a stereotropic reaction,⁹ it cannot take place without the presence of a solid base that furnishes a support for the migrating cells. In mice treated with various carcinogenic agents including benzpyrene, Orr¹⁰ observed transformation of the collagen of the dermis into a fine-fibered type and also alterations in the texture of the elastic tissues of the cutis. Such changes at the wound base might not only inhibit the migration of the epidermal cells but might also facilitate the downgrowth of the proliferating epithelium into the underlying tissue. However, further investigations will have to test the correctness of this assumption.

In the nonexcised epidermis, we noted a slow, gradual stimulation of the epithelium, when mitoses were counted in a given number of basal cells. The temporary depression of mitotic proliferation found by Champy and Vasiliu¹¹ in tarred mice and by Cooper and Reller¹² in mice painted with methylcholanthrene may be due to their method of counting.

The normal skin of mice shows not only a diurnal rhythm of proliferation, but also a constant transformation of mitotically proliferating basal cells into spinous cells that no longer undergo mitotic division. The spinous cells have lost their proliferative power, probably because they are removed further from the subcutis, their source of nourishment. In the normal epidermis of the mouse, the ratio of basal and spinous cells is 2:1 to 3:1. In the course of 2 months of treatment with benzpyrene, and incidentally with benzene also, this ratio changes to 1:1.3 in favor of the nonproliferating cells of the surface of the skin (Table IV). If the latter cells are excluded from the count, the mitotic index in the basal cells is found to increase steadily under the influence of benzpyrene.

SUMMARY

In the skin of normal mice, wound repair takes place primarily by proliferation and hypertrophy of the epidermis adjoining the wound and by movement of the epithelium into the defect. These processes are hastened by the application of benzene to the skin previous to the making of the wound. Under the influence of benzpyrene applied for 2 weeks previous to excision, both components of wound healing are likewise accelerated. After prolonged treatment with benzpyrene, proliferation of the epidermal cells is further intensified, whereas cell migration into the defect is inhibited or almost suspended.

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THE DEVELOPMENT OF HEPATIC CIRRHOSIS IN DOGS AFTER HYPOPHYSECTOMY

ITS ASSOCIATION WITH UNANTICIPATED, COINCIDENTAL HYPOTHALAMIC INJURY *

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During the course of studies on the influence of hypophysectomy on experimental renal hypertension in dogs, post-mortem examination revealed fatty cirrhosis of the liver in 3 animals. Thereafter another animal with early cirrhosis was encountered in Dr. Maurice Bodo's colony of hypophysectomized dogs and all four instances were reported briefly in 1939.¹ Since then another hypophysectomized dog with cirrhosis was encountered by Dr. Allen Keller at the University of Alabama, and he has kindly permitted us to include his case in this report.

When presumably comparable dogs were examined and no hepatic changes were observed, and it appeared unlikely that reduction or ablation of the hypophysis was related to the hepatic changes, further study was undertaken to find some other possible basis for the hepatic changes. Fifteen additional hypophysectomized dogs were available through those provided by Drs. Bodo and Shannon and one of us (I. H. P.). Hepatic fibrosis occurred in one instance that will be described later. However, few of the additional dogs were kept alive beyond 6 months and only 3 beyond 1 year. In this paper we are reporting the detailed findings in the 5 cirrhotic and, in addition, 6 noncirrhotic dogs, including among the latter 2 surviving $3\frac{1}{2}$ to $5\frac{1}{4}$ years.

Special attention was directed to the diencephalon because of its important rôle in many vegetative functions and in certain aspects of metabolism. The possibility of a neuropathologic basis for hepatic changes gains further support from the occurrence of Wilson's disease in man (lenticular degeneration and hepatic cirrhosis) as well as the occurrence of fatty livers in certain neuropathologic states.^{2, 3}

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MATERIAL AND METHODS OF STUDY

The animals were chiefly adult mongrel dogs from the city of New York, maintained on an abundant diet of hospital scraps (meat scraps and bones, bread, vegetables); to some, Purina dog biscuits were given daily and meat three times weekly. Hypophysectomy was performed on most of the animals by Dr. Joshua E. Sweet, using a subtemporal approach.⁴ This consists of the removal of the zygomatic arch by subperiosteal resection of the coronoid process close to the base. The skull is then trephined and the dura removed. The extirpation of the pituitary body is accomplished with the aid of a double spoon or curette. Rotation of the spoon after its edge is inserted underneath the pituitary capsule removes the gland and transects the infundibular stalk. Other surgical and experimental procedures related to the production of hypertension are noted in Table I-A.

The dogs furnished by Drs. Keller and Shannon were mongrels from Birmingham, Alabama, and had been subjected to transection of the pituitary stalk with hypophysectomy by the nasopharyngeal route.

In addition to the brains of the 11 animals that had been operated upon, those of 4 additional dogs were examined. Two were from animals dying during unrelated experiments, and 2 were from animals that died during renal hypertension. One of the latter dogs appeared to be in uremia at the time of death. All served as controls in standardizing the neuropathologic study, and the hypertensive animals also served as controls for the influence of hypertension. There were no pathologic changes in the pituitary gland or the hypothalamus.

The brains were fixed in 10 per cent Formalin (4 per cent solution of formaldehyde), after macroscopic examination. The tissue chosen for study was a block including the hypothalamic region; it was limited anteriorly by the rostral part of the optic chiasma, posteriorly by the caudal portion of the mammillary bodies. Laterally it extended to the level of the temporal poles and superiorly to the floor of the lateral ventricles, or to the outer surface of the cortex in 3 dogs. Serial celloidin, paraffin, or frozen sections were cut. For study of nerve cells and Nissl bodies the Nissl method was used. Myelinated nerves were stained with Loyez'^{4a} or Weil's method. As general stains, hematoxylin and eosin, Masson's trichrome stain, and Mallory's phosphotungstic acid hematoxylin were used. Prussian blue and mucicarmine stains were employed occasionally for demonstration of iron or mucin. Frozen sections of the liver were stained for fat with Sudan IV, and paraffin sections were stained by a variety of connective tissue stains. The sella turcica and covering dura mater of 7 dogs were examined in serial sections for pituitary remnants after decalcification. In the other 4

dogs only the remainder of the infundibular stalk was available for such study; the sella turcica had been inspected but not saved.

RESULTS

Tables I-A and I-B present a summary of the clinical and pathologic findings in the 5 animals with cirrhosis examined from 4½ months to 3 years after hypophysectomy. Tables II-A and II-B are based on 6 animals without cirrhosis examined from 10 months to 5¼ years after the operation. Since the findings reported here were not anticipated, there are many deficiencies in our clinical data and some in our post-mortem material. In a few animals, however, special attention was paid to symptoms and changes reflecting hypophyseal or hypothalamic injury, and the available notes are recorded in each table.

Generalized obesity was observed during the post-operative course of 8 dogs. It did not appear in 2 dogs, surviving only 10 days and 1 month respectively, or in 1 dog surviving 6 months. The fur of the 9 animals surviving 4½ months or longer became soft and luxuriant. No changes were observed in the coats of the 2 animals surviving 10 days and 1 month respectively. Diabetes insipidus was of variable onset, degree and duration in 8 dogs, all surviving 4½ months or longer. It was absent in 1 dog surviving hypophysectomy for 8 months and did not appear in the dog surviving 10 days, or in the dog surviving 1 month. These and the visceral findings are analyzed separately in the following sections. Correlations were made with the extent of the hypophysectomy and any coincidental hypothalamic lesions.

Liver

The lesions in the dogs with cirrhosis (Table I-A) varied considerably (Figs. 1 to 6). The mildest change was found in dog 4, sacrificed 11 months after operation. There was widespread fatty infiltration of the liver and on section increased lobular marking, suggestive of early cirrhosis, was visible (Fig. 3). Histologic study revealed a general increase of portal and periportal connective tissue with strands of young cellular connective tissue surrounding the hepatic lobules (Figs. 4 and 5). The latter appeared somewhat smaller than in comparable normal animals.

The remaining four livers were reduced in size and had macroscopic nodular cirrhosis, and protruding nodules of yellow tissue were visible through Glisson's capsule. All four also showed marked fatty deposit (neutral fat) in the parenchyma. The deposits of connective tissue were irregular (Figs. 2 and 6), being both monolobular and multi-lobular, involving the portal areas preponderantly in some portions, and irregularly traversing the parenchyma in others. No signs of recent

TABLE I-A
Clinical-Pathologic Observations on Cirrhotic Dogs

Experimental procedures			Clinical notes				
Dog no. and sex	Survival time after hypophysectomy	Renal and other	Changes in weight	Diabetes insipidus	Estrus	Miscellaneous	Hypertension
1 F	3 yrs., 7 mos. Operated upon, 1/36; sacrificed, 8/39	Rt. artery clamp, 11/35 Lt. artery clamp, 2/36 Bilat. oophorectomy, 1/37 Rt. nephrectomy, 6/38 Liver taken for biopsy, 8/39	Initial wt., 11 kg.; no wt. gain until spaying, then rose to 12.8 kg.	Polyuria for a few weeks after hypophysectomy	Ceased	Insulin reaction not tested; no convulsion observed	Transitory after June, 1938
2 M	2½ yrs. Operated upon, 10/35; died, 4/38	Rt. artery clamp, 9/35 Lt. artery clamp, 10/35	Initial wt., 13 kg.; postoperative gain up to 17 kg.	Permanent		Insulin reaction not tested; no convulsion observed	Present before hypophysectomy; transitory for 3 mos. after, and ceased
3 F	2½ yrs. Operated upon, 11/35; died, 3/38	Rt. artery clamp, 9/35 Lt. artery clamp, 12/35	Initial wt., 9.5 kg.; max. wt., 14.6 kg.; wt. at death, 13.9 kg.	Permanent, 0.4 to 0.6 liters output daily	Ceased	Convulsions on several occasions, unrelieved by intravenous glucose	Present before hypophysectomy; fell after to range of 140-160 mm. Hg
4* F	11 mos. Operated upon, 11/37; sacrificed, 10/38	None	Initial wt., 8 kg.; increased and remained at 9.75 kg.	Temporary and severe for 2 mos.	Ceased	Increased sensitivity to insulin	No data
5† F	4½ mos. Operated upon, 5/39; died, 10/39	None	Initial wt., 10 kg.; gain to 13.6 kg. at death	Delayed onset of mild and permanent type	Ceased	Insulin reaction not tested	No data

*From Dr. Bodo

†From Dr. Keller

degenerative or inflammatory alterations were found in four. In dog 4 a single microscopic focus of suppuration was encountered in one of five blocks. No bacteria were demonstrable in paraffin sections stained with Giemsa's stain.

The larger and smaller bile ducts and portal veins were unaltered. The smaller radicles were caught in the proliferated connective tissue. In some places remnants of lobules were discerned but their constituent

TABLE I-A
Clinical-Pathologic Observations on Cirrhotic Dogs

Significant post-mortem visceral findings				
Adrenal	Gonads	Liver	Thymus	Spleen
Mild cortical atrophy, with moderate lipid depletion; atrophy affects reticular zone	Not examined (removed 1 yr. after hypophysectomy and 2½ yrs. before death)	Unevenly distributed, sometimes multilobular, monolobular cirrhosis, chiefly portal; accompanied by reduction in size of the liver; irregular contraction of liver lobules and condensation of portal canals; some proliferation of bile ductules; marked increase of collagenous fibers; no inflammatory or necrotizing changes; moderate deposits of neutral fat globules in all lobules	Not examined	Marked atrophy of malpighian bodies and pulp cells
Marked cortical atrophy; only glomerular zone and few cells of fascicular zone preserved	Resting testis; no spermatogenesis beyond formation of spermatocytes	Widespread, monolobular and multilobular cirrhosis accompanied by marked deposits of neutral fat in liver cells; no inflammatory or necrotizing changes; considerable iron-containing pigment stored in macrophages in the proliferated connective tissue	Hyperplastic	Marked atrophy of malpighian bodies and pulp cells
Marked cortical atrophy; only glomerular zone and few cells of fascicular zone preserved	Prepubertal appearance of ovaries with many primordial follicles showing partial maturation	Diffuse monolobular and multilobular cirrhosis; fatty change marked in parenchyma; condensation of portal canals apparent in some areas; bile duct proliferation not definite; no inflammatory changes; mild focal bile and iron pigment storage	Persistent, uninvolved	Marked atrophy of malpighian bodies and pulp cells
Marked cortical atrophy; only glomerular zone and few cells of fascicular zone preserved	Marked replacement fibrosis of ovary	Early monolobular cirrhosis; marked fatty deposit in trabeculae; periportal fibrosis moderate with little extension around lobules; one focus of "sterile" suppuration; focal bile duct proliferation	Hyperplastic	No atrophy
Contracted; no microscopic study	Ovary normal macroscopically; no microscopic study recorded	Macroscopically yellow and with prominent lobular markings, monolobular and multilobular cirrhosis; marked fat deposition in persistent parenchyma; no definite bile duct proliferation; no recent degenerative or inflammatory changes; no pigment storage	No observations	No observations

trabeculae appeared narrow, short and atrophic in spite of considerable amounts of fat within the parenchymal cells. Masses of greenish brown pigment were found as plugs in some bile canaliculi but this was an inconstant finding limited to dogs 1 and 3. Iron-containing pigment, stored in macrophages, was found in the portal areas or in Kupffer cells in 2 of the other dogs with cirrhosis. Similar pigment storage is not uncommon in "normal" street dogs in our experience. Proliferation

of the smaller bile ducts was also inconstant; it was seen as part of the cirrhotic process in 3 and it was doubtful or absent in the others.

In the proliferated connective tissue other types of cells were rare. Macrophages with iron-containing pigment, histiocytes and, very rarely, lymphocytes were sometimes found.

No special manifestations of hepatic dysfunction were observed in any of the animals. Neither ascites nor icterus had been observed.

There was no correlation between the occurrence of cirrhosis and the completeness of the hypophysectomy; in 2 dogs (3 and 4) no pituitary remnants were found, while in the other 3, microscopic remains were present varying from clusters of anterior pituitary cells in the adjacent dura to most of the pars tuberalis. It was estimated that 90 per cent or more of the pars glandularis was removed in each instance.

Length of survival after complete or incomplete hypophysectomy bore no special relation to the extent of the hepatic lesions, for fatty cirrhosis that was macroscopically visible was found after 4½ months in 1 animal (dog 5), and a less advanced hepatic lesion was found in

TABLE I-B
Neuropathologic Status in Cirrhotic Dogs

Dog no. and sex	Time after hypophysectomy	Post-mortem state of hypophysis	Hypothalamus
1 F	3 yrs., 7 mos.	Considerable acinar pituitary tissue of the pars tuberalis remains attached to the infundibulum	Besides diminution of cells in supra-optic nuclei, there is an erosion of the hypothalamus, extending up to the fornix on the right side. The n. ventro-medialis, periventricularis arcuatus, posterior portion of anterior hypothalamic area, medial and inferior portions of lateral hypothalamic area, are included. Defect crosses the midline and includes left n. ventro-medialis and periventricularis arcuatus. It diminishes in width and depth anteriorly towards optic chiasma and posteriorly towards mammillary bodies. On the left, the erosion leaves medial eminence intact.
2 M	2 yrs., 6 mos.	Clusters of chromophobic cells can be seen in some sections through the infundibulum	There is reduction in number of cells of supra-optic nuclei and an erosion is present in the inferior part of the hypothalamus, affecting the medial and inferior portions of right n. ventro-medialis and left n. periventricularis arcuatus, and n. ventro-medialis. At some levels the eminentia medialis and inferior part of wall of 3rd ventricle are eroded. Erosion consists of small cavities containing calcific deposits. Defect is covered by connective tissue continuous with dura of sella turcica.

another (dog 4) after 11 months. However, the 3 animals surviving $2\frac{1}{2}$ years or more had nodular cirrhosis.

In the noncirrhotic group (Table II-A) the livers had minimal alterations; in 4 dogs the liver lobules seemed smaller because of closer approximation of the portal areas, suggestive of beginning condensation fibrosis, but no increase of connective tissue was found. The hepatic trabeculae appeared narrower. In 1 animal ($3\frac{1}{2}$ years after hypophysectomy) mild proliferation of bile ducts was found in the absence of any other change. Except for focal deposits in one liver, fatty deposition was notably absent.

Similar lack of correlation between completeness of hypophysectomy and hepatic status was noted in the noncirrhotic dogs. The liver was apparently normal after complete hypophysectomy in 1 animal (dog 6) surviving $5\frac{1}{4}$ years.

Another dog with only tiny microscopic clusters of residual pituitary tissue, surviving $3\frac{3}{4}$ years, developed minimal change in the liver consisting of a slight increase of periportal connective tissue without

TABLE I-B
Neuropathologic Status in Cirrhotic Dogs

Schematic drawings* to show the approximate location of the lesions in the hypothalamus from coronal (dogs 1, 2, 4) and sagittal sections (dogs 3, 5). Coronal drawings are shown with right side on the reader's left. Inclined lines on the drawings of sagittal sections represent levels at which coronal sections were made in the other dogs.

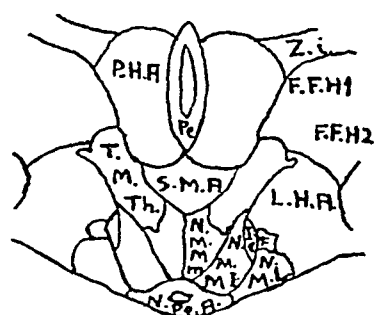
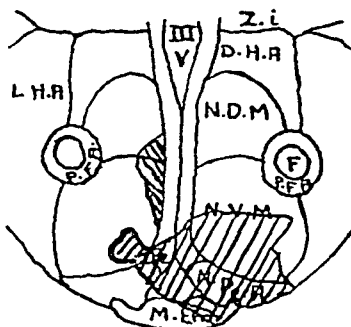
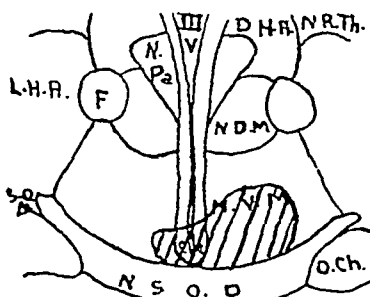
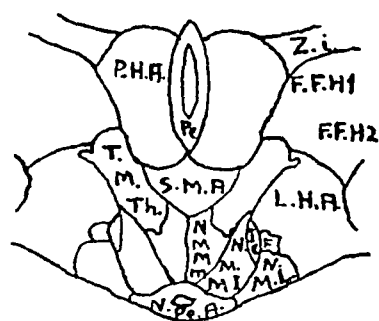
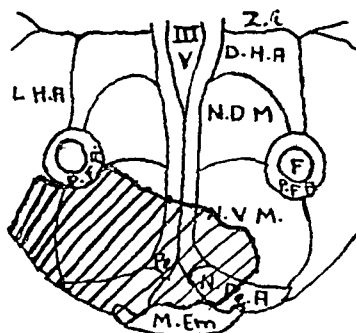
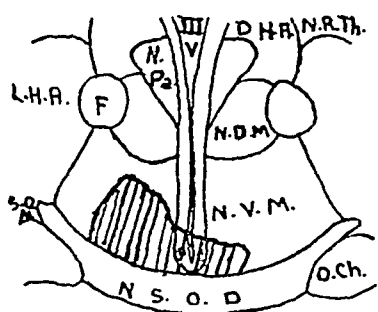


TABLE I-B (continued)

Dog no. and sex	Time after hypophysectomy	Post-mortem state of hypophysis	Hypothalamus
3 F	2 yrs., 4 mos.	No pituitary tissue found	An erosion is present between the optic chiasma and mammillary bodies. It includes the n. periventricularis arcuatus, ventro-medialis, and medial portions of the lateral hypothalamic area. There is diminution of cells in the supra-optic nuclei.
4 F	11 mos.	No pituitary tissue found; operative specimen includes pars glandularis	A defect is found involving the inferior part of the floor of the 3rd ventricle and the infundibulum on both sides. The n. periventricularis arcuatus, both n. ventro-medialis and the most medial part of the lateral hypothalamic area on the right are included. There is reduction of cells in the supra-optic nuclei.
5 F	4½ mos.	Nests of chromophilic pituitary cells (eosinophils) and chromophobes in the dura covering the pituitary fossa, reported by Dr. Keller	The hypothalamus shows an erosion which extends to the supra-optic nuclei and the nuclei ventro-medialis, the dorso-medialis, and the periventricular arcuatus on both sides.

* Nomenclature is that given in "The Hypothalamus," published by the Association for Research in Nervous and Mental Diseases, Williams & Wilkins Co., Baltimore, 1940.

L.H.A.—Lateral hypothalamic area

F—Fornix

N.D.M.—Nucleus dorso-medialis

N.V.M.—Nucleus ventro-medialis

S.O.N.—Supra-optic nucleus

N.S.O.D.—Nucleus supra-opticus diffusus

O.Ch.—Optic chiasma

N.Pa.—Nucleus paraventricularis

Pe.—Periventricular system

P.F.A.—Perifornical area

D.H.A.—Dorsal hypothalamic area

N.R.Th.—Nucleus reticularis thalami

III V.—Third ventricle

Z.I.—Zona incerta

M.Em.—Median eminence

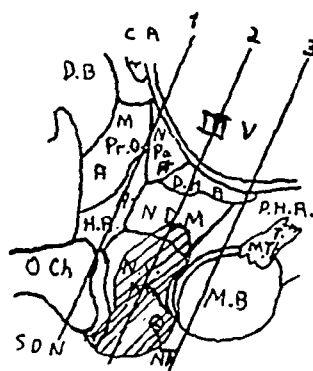
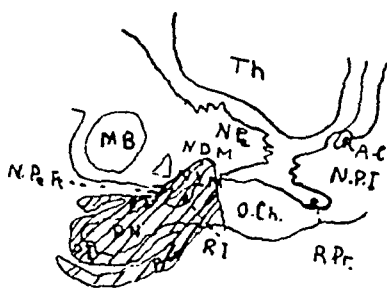
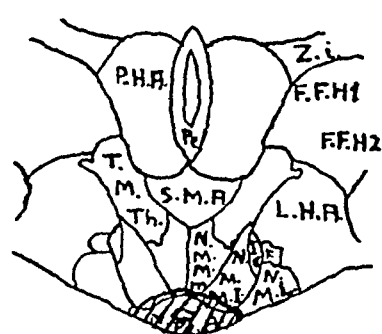
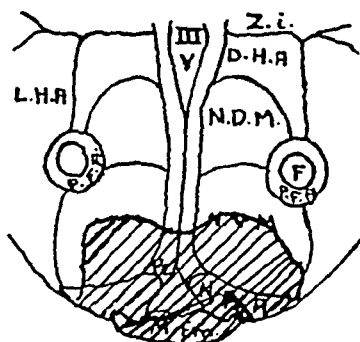
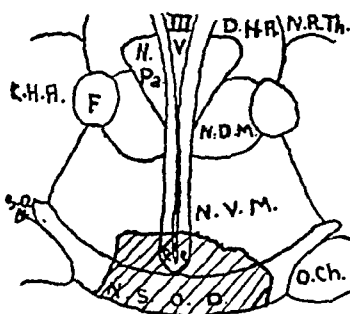
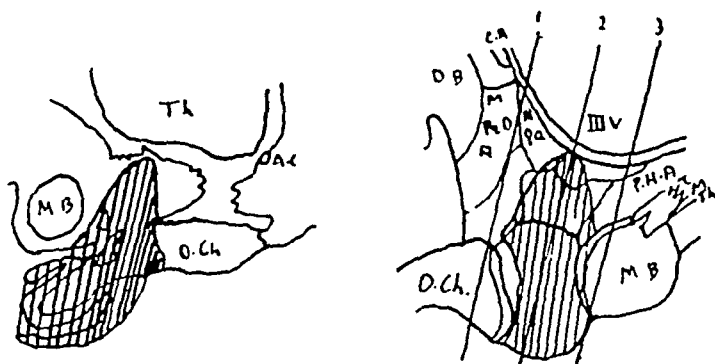
N.Pe.A.—Nucleus periventricularis arcuatus

PH.A.—Posterior hypothalamic area

F.F.H₁, H₂—Field of Forel H₁, H₂

TABLE I-B (continued)

Schematic drawings* to show the approximate location of the lesions in the hypothalamus from coronal (dogs 1, 2, 4) and sagittal sections (dogs 3, 5). Coronal drawings are shown with right side on the reader's left. Inclined lines on the drawings of sagittal sections represent levels at which coronal sections were made in the other dogs.



T.M.Th.—Mammillo-thalamic tract
S.M.A.—Supramammillary area
N.M.Mm.—Nucleus mammillaris medialis (pars medialis)
N.M.Ml.—Nucleus mammillaris medialis (pars lateralis)
N.M.L.—Nucleus mammillaris lateralis
I.C.—Nucleus intercalatus
M.B.—Mammillary bodies
R.Pr.—Recessus preopticus

A.C.—Commissura anterioris
Th.—Optic thalamus
R.I.—Recessus infundibularis
P.N.—Pars nervosa
P.I.—Pars intermedia
P.G.—Pars glandularis
P.T.—Pars tuberalis
M.Pr.O.A.—Medial preoptic area
N.P.I.—Nucleus preopticus internus
D.B.—Diagonal band

TABLE II-A
Clinical-Pathologic Observations on Noncirrhotic Dogs

Dog no. and sex	Experimental procedures		Clinical notes				
	Survival time after hypophysectomy	Renal and other	Changes in weight	Diabetes insipidus	Estrus	Miscellaneous	Hypertension
6 F	5¼ yrs. Operated upon, 1/36; sacrificed, 3/41	Rt. artery clamp, 3/35 Nephrectomy, lt., and adrenalectomy, lt., 4/35	Initial wt., (?); animal became obese and continued to gain before sacrifice	Mild, lasting 3 yrs.	Ceased	Insulin reaction not tested; spontaneous convulsion occurred once in 10/39	Modest, and maintained through 1939
7 F	3¾ yrs. Operated upon, 4/37; sacrificed, 1/41	Rt. artery clamp, 10/36 Lt. artery clamp, 10/36 Rt. artery clamp removed, 1/37 Lt. artery clamp removed, 2/37 Liver taken for biopsy, 8/39	Initial wt., (?); animal became obese and indolent	Moderate for 3½ yrs.	Ceased	Insulin reaction not tested; spontaneous convulsion occurred once in 1/40	From 2/37 to 4/37
8 M	8 mos. Operated upon, 6/39; died, 2/40. Cause: malignant hypertension	Rt. nephrectomy, 12/39 Lt. kidney wrapped in cellophane, 1/40	Initial wt., 10 kg.; 6 and 8 mos. after hypophysectomy, 11.5 and 12.8 kg. respectively	Absent (?)		Insulin reaction not tested; no convulsions observed; necrotizing arteriolitis in G.I. tract	Appeared 25 days before and was sustained
9 F	6 mos. 8 days Operated upon, 6/39; died, 12/39. Cause: malignant hypertension	Rt. kidney wrapped in cellophane, 8/39 Lt. kidney wrapped in silk, 9/39	None observed	Permanent	Not observed	Insulin reaction not tested; retinal detachment; renal insufficiency	Moderate, observed from 9/39 to 11/39
10 M	1 mo., 5 days Operated upon, 6/39; died, 7/39 Cause (?)	Lt. kidney wrapped in cellophane, 4/39	None	Not observed; no measure of intake and output of fluids		Insulin reaction not tested; no convulsions observed	4/28 to 6/15/39
11 M	10 days Operated upon, 9/30; died, 10/39. Cause: meningoencephalitis (?)	Kidneys denervated and wrapped with cellophane: rt., 10/38; lt., 1/39 Rt. nephrectomy, 4/39 Lt. kidney explanted, 5/39	None	Did not develop		Insulin reaction not tested; spontaneous convulsion occurred once in 10/39	Present from 1/19 to 4/18/39

TABLE II-A
Clinical-Pathologic Observations on Noncirrhotic Dogs

Significant post-mortem visceral findings				
Adrenals	Gonads	Liver	Thymus	Spleen
Lt. removed Rt. normal	(?)	No visible fat; apparently normal	Persistent, uninvoluted	No atrophy No fibrosis
Marked cortical atrophy	Fibrous replace- ment of ovaries	Very mild proliferation of bile ducts and connective tissue, otherwise normal; no visible fat	Persistent, uninvoluted	No atrophy No fibrosis
Grossly atrophic; not examined microscopically	Resting testis; spermatogonia show active divi- sion but sperma- tids absent	Mild lobular atrophy with moderate trabecular atrophy; widening of liv- er sinusoids and condensation of portal canals; fatty infiltration found in small zones in an occasional lobule	Uninvoluted, (hyperplastic ?)	No atrophy No fibrosis
Mild cortical atrophy affect- ing juxtamed- ullary zone	Active maturation of follicles; corpus luteum present; many primordial follicles visible	Irregular zonal atrophy; widespread focal periportal cellular infiltration; no definite fibrosis; no fatty infiltra- tion	Not examined	No atrophy, active hemopoiesis, no fi- brosis or chronic passive congestion
Grossly normal	Resting testis; in- terstitial cells scanty	Lobules somewhat reduced in size and liver cords are short and narrower than normal; no fatty infiltration; no increased fibrosis	Not found	No atrophy, no fi- brosis or chronic passive congestion
Grossly normal; no sections available	Spermatocytes ac- tive in division; no spermatids in many tubules	Widespread narrowing of liver trabec- ulae but early stages of post-mortem autolysis are found in some lobules; no inflammatory changes; no fatty infiltration	Not found	No pigment storage or atrophy

TABLE II-B
Neuropathologic Status in Noncirrhotic Dogs

Dog no. and sex	Time after hypophysectomy	Post-mortem state of hypophysis	Hypothalamus
6 F	5¼ yrs.	Nests of chromophilic cells (eosinophils) and chromophobic cells were found in the dura beneath the tuber cinereum	No pathologic findings encountered in serial coronal sections except diminution of cells in supra-optic nuclei.
7 F	3¾ yrs.	Remnants of anterior pituitary cells (chromophilic alpha-cells and chromophobes are attached to the infundibulum)	There is diminution of cells in supra-optic nuclei. The most distal portion of the eminentia medialis, attached to the infundibulum, is separated from the rest of the brain. Lateral to this defect there is considerable increase in meningeal connective tissue, particularly rich in mononuclear cells with eosinophilic granules.
8 M	8 mos.	Attached to the infundibulum there are remnants of pituitary tissue consisting of chromophobes and eosinophilic granular cells	A defect of nerve substance affects the floor of the 3rd ventricle, from the level of the midline of the mammillary bodies to the anterior aspect of the infundibulum; it includes the wall of the 3rd ventricle and extends, on the right at some levels, to the medial part of the lateral hypothalamic area, through the n. ventromedialis and dorso-medialis and periventricularis arcuatus. Definite reduction of cells of supra-optic nuclei has occurred.
9 F	6 mos., 8 days	There are remnants of pituitary tissue attached to the infundibulum, represented by chromophilic (eosinophils) and chromophobic cells	A small erosion was found completely destroying the eminentia medialis. It extends to and opens the cavity of the third ventricle in the midline. There is apparent diminution of cells in the supra-optic nucleus.

TABLE II-B
Neuropathologic Status in Noncirrhotic Dogs

Schematic drawings* to show the approximate location of the lesions in the hypothalamus from coronal sections through the diencephalon. Drawings are made with right side depicted on reader's left.

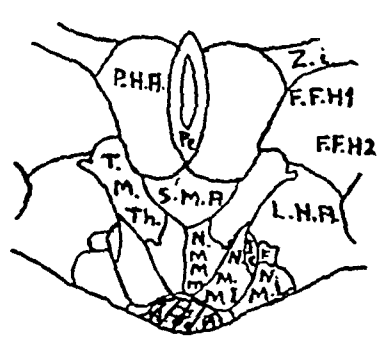
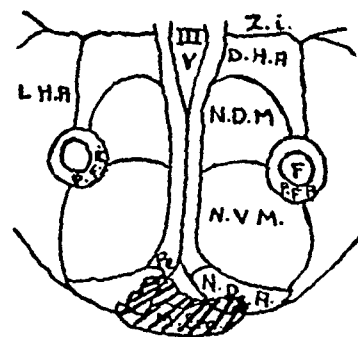
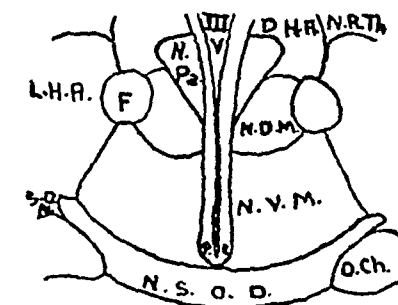
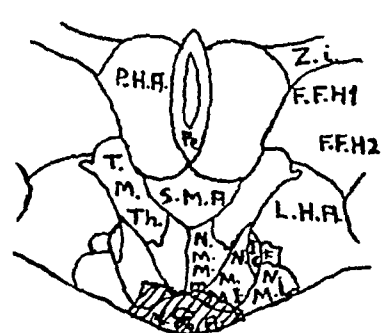
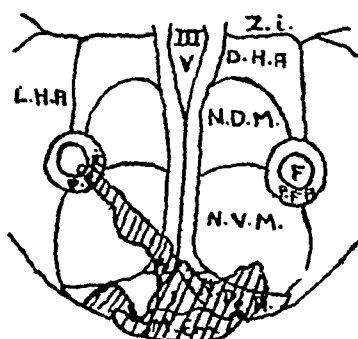
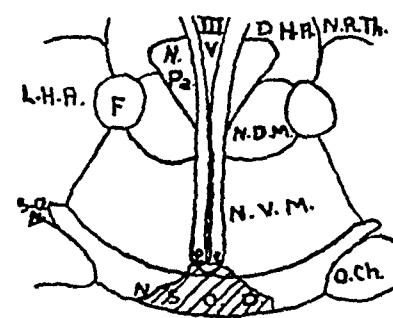
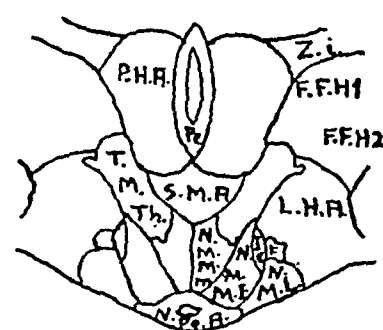
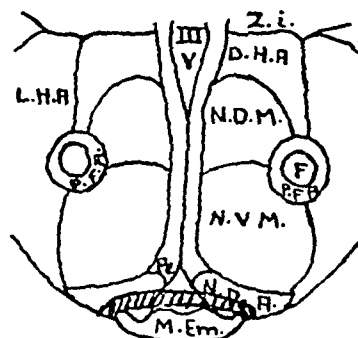
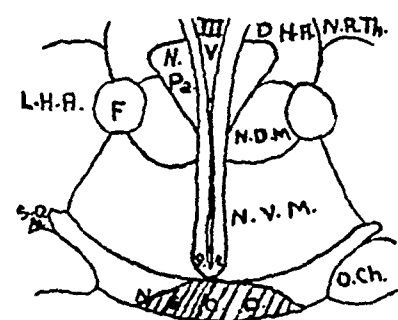
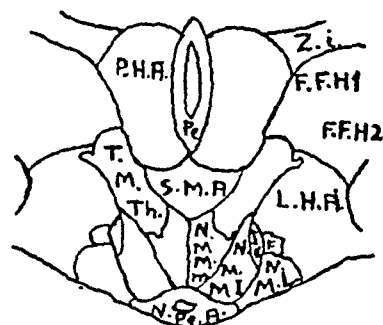
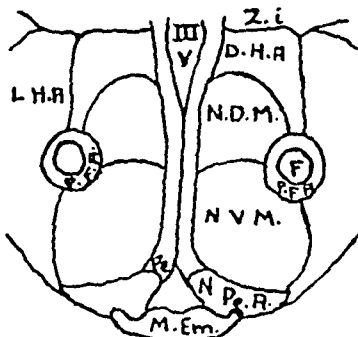
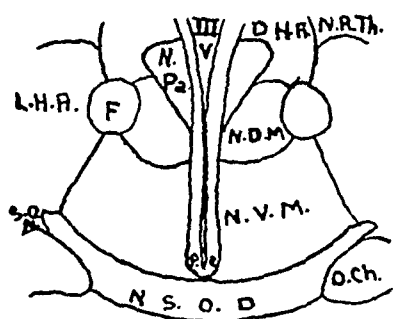


TABLE II-B (continued)

Dog no. and sex	Time after hypophysectomy	Post-mortem state of hypophysis	Hypothalamus
10 M	1 mo., 5 days	No pituitary tissue was found in the membranes attached to the external surface of the hypothalamus; sella turcica not examined	There is a defect in nerve substance in the middle of the floor of the 3rd ventricle including the ventro-medialis, periventricular arcuatus, and the inferior part of the walls of the 3rd ventricle. There is apparent diminution of cells of the supra-optic nuclei on comparison with normal.
11 M	10 days	No pituitary tissue was found in the membranes covering the external surface of hypothalamus; sella turcica not examined	Perivascular infiltration of lymphocytes and some plasma cells were found in different areas of the brain and meninges. There were also small, widely scattered areas of demyelination. These findings were interpreted as evidence of meningo-encephalitis of undetermined etiology probably induced by operation.

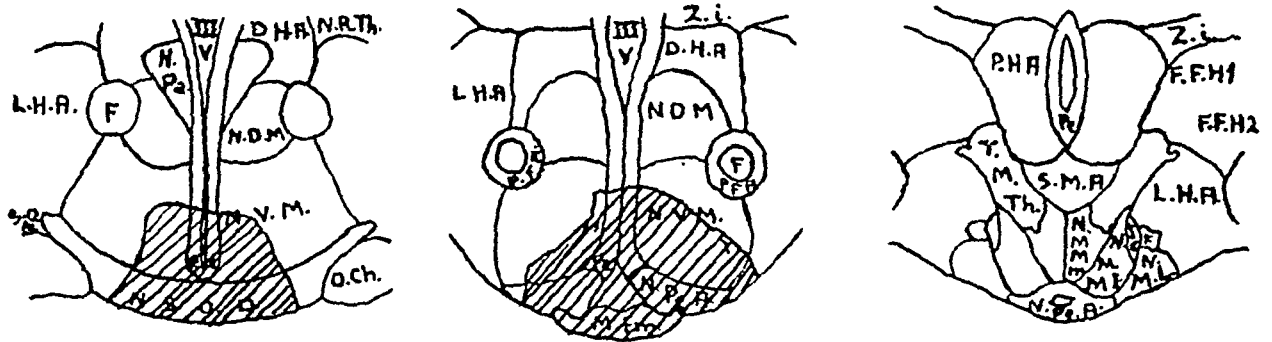
fatty deposits. Pituitary remnants were found in 2 dogs surviving 6 and 8 months (dogs 9 and 8). In the other 2, surviving 10 days and 1 month, no pituitary remains were noted in the connective tissue covering the external surface of the hypothalamus, but the sella turcica was not studied in serial sections.

On analysis of the hypothalamic lesions (Table I-B) positive correlation is noted with respect to the occurrence of fatty cirrhosis and the finding of extensive defects of the hypothalamus (see schematic drawings and Figs. 9 to 12). The defects seem to be attributable to the operation. Lesions vary somewhat from case to case, but in each there were irregular defects of brain substance, with or without reaction, usually involving the nuclei * ventro-medialis on both sides, periventricularis arcuatus, and parts of surrounding hypothalamic structure. In all, the supra-optic nuclei showed reduction of the number of their cells independent of proximity to defects of the hypothalamus.

By comparison, the hypothalamic lesions were not nearly so extensive in the noncirrhotic dogs (Table II-B) with relatively normal livers. In dog 6, surviving $5\frac{1}{4}$ years, there was no defect except diminution in cells of the supra-optic nuclei—a change to be expected after transection of the pituitary stalk.⁵ In dog 7, surviving almost 4 years, minimal hypothalamic injury was discerned consisting only of a micro-

* Terminology is that recommended in *The Hypothalamus. A. Research Nerv. & Ment. Dis., Proc.*, 1940, 20.

Schematic drawings* to show the approximate location of the lesions in the hypothalamus from coronal sections through the diencephalon. Drawings are made with right side depicted on reader's left.



* Abbreviations are as given in footnote to Table I-B.

Adrenals

In 3 animals (dogs 3, 4 and 6) with varying degrees of adrenal atrophy, no pituitary remnants could be found upon examination of

serial sections through the sella turcica. One of these (dog 6) had had a unilateral adrenalectomy prior to hypophysectomy but the cortex of the surviving gland was regarded as slightly atrophic. The liver was normal. Two other dogs (dogs 2 and 7), with more marked adrenal atrophy, had microscopic nests of anterior pituitary cells attached to the meninges overlying the hypothalamus. In 1 dog the liver was not abnormal (dog 7), in the other it was cirrhotic (dog 2). Less marked adrenal cortical atrophy was noted in 2 other animals (dogs 1 and 9) and these had considerable residual pars tuberalis. In 2 additional dogs (dogs 5 and 8) with obviously smaller adrenal glands, microscopic pituitary remnants were found but the pars glandularis had been fully removed. The remaining 2 animals had normal adrenals but lived only 10 days and 1 month, respectively, after hypophysectomy.

In view of the inconstant atrophy of the adrenal glands, a correlation of this visceral change with the hypothalamic alterations was sought. This was further indicated because of the reports of splanchnomicria in human beings with hypothalamic injuries.¹⁰ The 6 animals with marked adrenal atrophy (dogs 2, 3, 4 and 7, verified histologically, and dogs 5 and 8 with grossly contracted glands) had different degrees of hypothalamic defects. They were fairly extensive in all but 1 (dog 7). But dog 1, with much of the pars tuberalis left (Figs. 9 and 10) had only moderate adrenal cortical atrophy although it also had an extensive hypothalamic defect. The 2 dogs that survived 10 days and 1 month did not have narrowing of the adrenal cortex, although they had hypothalamic defects and no infundibular pituitary rests. (The sella was not examined microscopically for pituitary cells.)

The coexistence of hypothalamic defects and ablation of the pars glandularis makes it impossible to relate the reduction of adrenal cortex to one procedure alone. There may be differences in the nature and mode of reduction of the adrenal cortex following hypophysectomy as compared with changes following hypothalamic injury, but the material is not suitable to establish this point.

Thymus

In 7 dogs, 4 of the cirrhotic animals and 3 of the noncirrhotic, the thymus was easily found. In 3 it was regarded as hyperplastic, in others merely as not involuted. This finding likewise could not be related to hypophyseal reduction alone because of the coincidental hypothalamic damage in all but 1 (dog 6). This dog, surviving hypophysectomy 5 years with minimal hypothalamic change (*i.e.*, reduction of cells of the supra-optic nuclei), illustrates the "thymus-stimulating" effect of this operation.

Spleen

There was evidence of chronic congestion of the spleen in 4 of the cirrhotic animals; the organ was not saved in the fifth. Of the 4, three spleens were contracted and histologic examination disclosed atrophy of the white and red pulp.

Obesity

Because the cirrhotic animals had notable fat deposits in the liver, correlation with the occurrence of generalized obesity was made. The 2 dogs surviving hypophysectomy only 10 days and 35 days did not gain weight. In another animal (dog 9) weight changes were not recorded, but it did not appear obese at necropsy 6 months after hypophysectomy.

General obesity and marked increase of weight were observed in 8 dogs, including all 5 with fatty cirrhosis and dogs 6, 7 and 8; of these all but 1 (dog 6) had lesions in the hypothalamus. Of the other 7, 5 (dogs 1, 2, 5, 7 and 8) had microscopic clusters of anterior pituitary cells; 1 had most of the pars tuberalis. But dogs 3 and 4 also became obese and had had complete ablation of the hypophysis with defects of the hypothalamus. It is noteworthy that dog 6, surviving $5\frac{1}{4}$ years with complete hypophysectomy and no hypothalamic injury, also became obese. It should be noted that these animals were confined in cages or kennels with small runs for most of their postoperative period. Lowering of the body temperature and reduction of the metabolism¹¹⁻¹³ consequent to the partial or complete ablation of the pars glandularis* of the hypophysis or hypothalamic injury¹⁴ may also have contributed to gain in weight. While it is notable that all 5 animals with fatty cirrhosis gained weight excessively, 3 other dogs with generalized obesity failed to show hepatic lesions excepting focal fatty change in 1.

Diabetes Insipidus

Lack of adequate clinical data precludes critical correlation and analysis of the time of occurrence, severity and duration of diabetes insipidus and the associated hypothalamic changes. However, no significant correlation could be found between diabetes insipidus and the occurrence of fatty cirrhosis. Diabetes insipidus was observed in 8 animals; it occurred with varying severity at different intervals after operation, and persisted for variable periods.

* Reports of the metabolic and thermal effects attributed to hypophysectomy alone have not been altogether satisfactory because of failure to examine or to record examination of the hypothalamus after the operation.

DISCUSSION

When hepatic cirrhosis was first encountered among these dogs, consideration was given to possible etiologic factors unrelated to the hypophysectomy. Dietary influences were first excluded since no similar hepatic lesions have been encountered in a very large number of dogs kept on the same diet, in the same laboratories, for as long a time, but not subjected to hypophysectomy. Vermifuges containing possible hepatic toxins, such as carbon tetrachloride, were never employed. Bacterial or parasitic infections were not found. The increase of connective tissue has not been accompanied by leukocytic infiltration of any type, or by new capillary formation except in one instance (dog 4) and in this animal it was a chance finding.

However, it may be of interest to mention 1 other dog that we examined at necropsy through the courtesy of Drs. Shannon and Keller. Dr. Shannon has reported clinical studies¹⁵ on this animal. It is not included in our tables because the pituitary gland was not removed, although transection of the pituitary stalk was performed together with destruction of a considerable area of contiguous hypothalamic tissue. The animal died 2 years after the operation and the only significant post-mortem visceral finding was diffuse suppurative and interstitial hepatitis, associated with wide zones of contraction and atrophy of the parenchyma. Only moderate, irregularly distributed deposits of lipid globules could be found in the intact liver cells. No inflammatory changes were found in the gallbladder, biliary passages, or the blood vessels. No organisms were demonstrated in the lesions. The lesions were classified as probably infectious in origin, although the possibility of subacute yellow atrophy has also been kept in mind. No operation other than the intracranial procedures had been done and the development of the severe hepatic lesions could not be related to any other events.

There seems little likelihood that the cirrhosis in the series of dogs reported here was spontaneous. In post-mortem examinations of about 300 dogs by one of us (I. G.) and of 3000 to 4000 dogs by another (I. H. P.), we have not encountered hepatic cirrhosis as a spontaneous lesion. In a personal communication, Dr. William Feldman of the Mayo Clinic stated that he has not found spontaneous hepatic cirrhosis in an equally large number of dogs. One of our animals had obvious cirrhosis only 4½ months after the intracranial operation and the time interval seems too short for the development of such an advanced lesion. Nevertheless, it had the most extensive hypothalamic defect in the series. The 5 animals with hepatic cirrhosis had, in common,

fatty deposits in the liver, adrenal cortical atrophy, involutional changes in the gonads, more or less complete hypophysectomy, and severe hypothalamic lesions. There were postoperative obesity, a change in their coats characterized by softness and luxuriant growth, and diabetes insipidus of varying severity. The absence of all or most of the anterior hypophysis may be held responsible for some of these changes but not for the hepatic lesion. We believe that the latter lesion can be more reasonably related to the hypothalamic defects.

Fat deposition in the liver after hypophysectomy was first attributed by Goetsch, Cushing and Jacobson¹⁶ to the accompanying general disturbance in lipid metabolism. With the development of better experimental technic it was later appreciated that general obesity and genital atrophy could be induced by hypothalamic defects alone.^{17, 18} Smith⁶ has shown that obesity does not follow simple ablation of the pars glandularis of the hypophysis. Furthermore, Chaikoff, Gibbs, Holtom and Reichert¹⁹ have reported that the hepatic lipids were in normal amounts up to 4 months after complete hypophysectomy in most of their dogs. However, one-third of them presented unexplained persistently high blood lipids. This point will receive further consideration later in this paper. In a study of the effects of hypophysectomy in puppies, Dandy and Reichert²⁰ reported cessation of growth, infantilism, and possible recession in size of the thyroid, sex glands and pancreas. They found no abnormalities in the livers of animals surviving as long as 2½ years. It is notable that none of their puppies became obese. Our own findings show that deposition of lipids in the liver is not inevitable after anterior hypophysectomy.

The early work attributing fatty deposit in the liver, like general adiposity, to the removal of the anterior lobe of the hypophysis must be qualified, therefore, by the knowledge that little or no attention was paid to the probable coexistence of injury to centers in the hypothalamus as an incidental result of the operation. Because of the short infundibular stalk, the extension of the tuber cinereum into it and its envelopment by the posterior, superior portion of the pars anterior, it is virtually impossible to perform an hypophysectomy in the dog without injuring the tuber cinereum (Van Dyke²¹). In our series only 1 dog (no. 6) escaped any detectable hypothalamic damage.

There is increasing evidence that fatty deposits in the liver may be related to hypothalamic lesions. Kraus^{2, 3} has claimed that fatty deposits, usually pericentral in location, occur in the liver of man in association with certain neurologic disturbances, notably cerebral tumors accompanied by increased intracranial pressure, in Cushing's syndrome, and especially in patients with lesions of the hypothalamo-

hypophyseal pathways. It is well known that lesions in the region of the tuber cinereum (due to encephalitis, tumors, hydrocephalus) may cause the syndrome of pituitary obesity (Erdheim,^{22, 23} Gottlieb,²⁴ Raab²⁵).

One of us (I. G.) has recently encountered two instances illustrating this point. One was of mammary carcinoma in a middle-aged woman with widespread metastases, including the pars nervosa of the pituitary gland, extending well up the infundibular stalk. The pars glandularis was unaffected histologically. The patient had retained mild obesity and developed severe diabetes insipidus 6 weeks before death. The liver had moderate deposits of neutral fat in the central three-fifths of each otherwise normal lobule. The other instance has been reported by Collins.²⁶ Through his courtesy we studied the histologic preparations from the organs of a woman, 25 years old, who had died in coma after a long illness. At necropsy a huge astrocytoma was found replacing the hypothalamus but sparing the anterior hypophysis. The viscera were small (notably the adrenal), and the liver had fatty deposits affecting four-fifths of each otherwise normal lobule.

Brobeck, Tepperman and Long²⁷ have recently recorded supporting observations in rats with experimental hypothalamic lesions. The frequent occurrence of fatty livers in their animals was striking. In a personal communication Dr. Tepperman stated: "We would like to emphasize the fact that all of the animals showing high blood and liver lipids were obese, and that (although our series was rather small) there seems to be a rough correlation between the level of liver fat and the degree of obesity. We have made no liver lipid determinations on animals whose food intake was limited to that of their controls. This is an important omission and we hesitate to ascribe any of the metabolic abnormalities we have seen to the hypothalamic lesion itself. We believe that many of the phenomena may prove to be attributable to changes in food habit produced by the lesions." If this idea is correct, the occurrence of fatty infiltration of the liver in the presence of hypothalamic lesions may be found to be unrelated to any direct nervous or hormonal influence on the liver and this important suggestion may furnish a clue for resolving the conflicting evidence and views on this subject. In the 11 dogs reported here, lipid deposit in the liver was found more often in the cirrhotic animals than in the noncirrhotic. Minimal hypothalamic injury was observed in the latter and especially in those dogs surviving 5 and 3½ years. The absence of such fatty deposits may be evidence in support of this hypothesis.

The appearance of fat in the cirrhotic livers of dogs may be a reflection of the tendency of that substance to accumulate in the cirrhotic

organ. Or it may reflect a basic disturbance in which both fatty deposits and fibrosis are related or independent manifestations. From the data in the tables presented here it does not seem likely that generalized obesity is responsible for fatty infiltration of the liver in this series of animals. It is noteworthy that some obese animals did not have significant amounts of microscopically visible fat in the liver.

Another factor needs to be discussed, namely, the possibility that splanchnomicria may contribute to atrophy of the liver cords, whether fatty or not, with a relative increase of fibrous tissue or an actual replacement fibrosis. Unfortunately we did not have hepatic weights in all of our animals or a standard of reference for normal dogs. Nevertheless, in the animals with mild cirrhosis that had hypothalamic defects, the hepatic lobules appeared to be reduced in size and the trabeculae seemed narrower than normal. Observations on rats that have a bearing on this point have been recorded by Lee and Ayres.²⁸ They noted shrinkage and loss of weight of the liver following hypophysectomy. Whether this was due to simple ablation of the anterior portion of the pituitary gland or to lesions in the hypothalamus is unknown. The splanchnomicria of Simmond's disease has usually been attributed to insufficiency of the pars glandularis. Evidence has been collected¹⁰ to show that the syndrome may occur with diencephalic lesions. The patient of Collins²⁶ is a case in point. In the presence of an intact anterior hypophysis there was marked atrophy of the thyroid, the adrenal glands, the ovaries and the endometrium.

A more closely allied disorder that reflects a neurohepatic relationship is seen in Wilson's disease (hepatolenticular degeneration). The explanation of the occurrence of cirrhosis of the liver in this disorder has not been forthcoming. Studies of the brain have shown that in the Wilsonian form the degeneration is limited to the globus pallidus. But degenerative processes in the lenticular nucleus may extend to the thalamus, the substantia nigra, the red nucleus and the cerebellum in the form called pseudosclerosis of Strümpell-Westphal. In both forms, because of direct connections by nerve fibers,²⁹ an effect on the hypothalamus may be expected even when it is not directly involved. It is well known that the hepatic disturbances begin after the onset of neurologic manifestations, even years after the first neurologic symptoms. Although microscopic deposits of fat globules are occasionally encountered in the liver cells, they have been apparently regarded as incidental findings.³⁰

It is not yet possible to draw conclusions concerning the neurologic factors operating in our dogs. The hypothalamic injuries involved tissues with unknown functional relations, among them groups of cells

designated as "nuclei," which were partly or completely removed. Except for the generally accepted rôle of the supra-optic nuclei in water metabolism, there are few satisfactory data concerning the function of the other "nuclei," although injury or deficiency may evoke striking changes. Furthermore, the injuries were seldom sharply localized; usually they extended irregularly from the surface of the hypothalamus inward and laterally. Future studies based on localized lesions may throw more light on these problems.

The cause of the increase of connective tissue in the livers of our dogs is equally obscure. This cirrhosis is similar to that reported in depancreatized dogs by Chaikoff, Connor and Biskind.³¹ Their animals developed fatty livers at variable periods after pancreatectomy. "In those kept for from 2.6 to 5.5 years upon an adequate diet and insulin, 8 of 16 developed more or less interlobular fibrosis of the livers. . . . In 4 animals this was so pronounced, both grossly and microscopically, that the picture of a well advanced portal cirrhosis of the liver was present. By the time this severe cirrhosis had occurred, the fat content of the livers had returned to normal and there was little histological evidence that a markedly fatty liver had preceded the fibrosis." These authors also could find no direct relationship between the interval after pancreatectomy and the degree of fibrous proliferation. One wonders why the other half of their animals failed to develop cirrhosis even though lipid in excess had been laid down in the liver. Incidentally, no pancreatic changes were found in our dogs. Connor³² also considered that the fatty liver of the alcoholic subject is an important preliminary stage in the development of portal cirrhosis.

The observations of Brobeck, Tepperman and Long,²⁷ relating obesity and hepatic lipids to disturbances in food habits secondary to experimental hypothalamic injury, point anew to the need for more information on the composition of the diet of experimental animals. In the light of their work any metabolic disturbance attributed to selective hypothalamic or pituitary injury must be re-examined with regard to the animals' diets. Their observations may furnish a clue to the previously unexplained high blood lipids in the hypophysectomized dogs of Chaikoff, Gibbs, Holtom and Reichert.¹⁹

The deposition of fat in the liver is still the subject of too much controversy to permit a positive statement as to the mechanism operating in our animals. The occurrence of fatty liver after certain diets,³³⁻³⁸ the augmentation of fatty deposits after pancreatectomy³¹ and the reports of hepatic necrosis or fatty cirrhosis developing after diets low in protein and fat^{39, 40} or low in protein and high in fat, as observed in rats⁴¹ and dogs,⁴²⁻⁴⁴ show how diverse diets may lead to superficially similar hepatic changes. The relation of hepatic necrosis or cirrhosis to

antecedent or concomitant fatty deposition remains unexplained. In a recent study of hypophysectomized rats given high fat or high carbohydrate diets, Samuels, Reinecke and Ball⁴⁵ found more body fat and less liver fat in the animals operated upon than in controls on the same caloric intake of a given diet. Lacking information of the exact composition of the diet of our dogs, we can only speculate as to possible deficiencies or excesses of individual constituents.

To recapitulate, it appears reasonable to conclude that hypophysectomy itself (or the operations on the kidneys in the animals with perinephritis) had little if anything to do with the hepatic lesions encountered in these dogs. The hypothalamic lesions disclosed by histologic examination seem to have a pivotal rôle in the hepatic changes. They were most extensive in the cirrhotic animals and were associated with the usual visceral effects encountered in hypothalamic injuries located in the same general vicinity. The adiposity of the cirrhotic animals reflected the metabolic changes, and in the light of the findings and suggestions of Brobeck, Tepperman and Long²⁷ they may be construed as evidence of the alteration of food habits of our dogs. We gave no especial attention to the diet of our animals. It may have provided a combination of fat and protein, with or without adequate proportions of essential amino acids or other substances likely to lead to fatty cirrhosis like that reported in dogs,^{41, 42} rats^{38, 39, 40, 44, 46} and rabbits⁴⁷ on improper diets. So-called "hospital scraps" were the principal sources of food in some of our dogs; Purina dog biscuits were given daily and meat three times weekly to most of them. It is possible that insufficient protein was given our animals. While it is noteworthy that a similar diet failed to induce fatty cirrhosis or fatty infiltration among the "control" animals, it seems reasonable to hypothesize that the cirrhotic dogs may have acquired fatty deposits because of excessive food intake, due to augmented appetites following the hypothalamic injuries.

CONCLUSIONS

1. Fatty cirrhosis of the liver was encountered in 5 dogs that had been hypophysectomized 4½ months to 3¾ years prior to post-mortem examination.
2. Six noncirrhotic animals examined 10 days to 5 years after hypophysectomy failed to exhibit fatty deposit or other hepatic change although moderate obesity was present in the animals surviving 8 months to 5 years.
3. Associated visceral and physiologic changes, such as adrenal cortical atrophy, thymic hyperplasia, coat changes, obesity, and diabetes insipidus, could not be related to the presence or absence of hepatic changes.

4. Study of the hypothalamus disclosed defects of variable position and extent in the cirrhotic animals that were invariably greater than in the control animals after hypophysectomy.

5. Consideration of the literature indicates that the variable reports of fatty infiltration of the liver after hypophysectomy did not take into account the rôle of associated, often unsuspected, hypothalamic injury. Furthermore, analysis of the results of uncomplicated hypophysectomy showed that obesity and fatty infiltration of the liver do not follow. In contrast, hypothalamic injury is regarded as probably responsible for the disturbance in metabolism and perhaps changes in food habits leading to obesity and fatty infiltration of the liver depending on the diet of the animal.

6. A hypothetical explanation is offered to account for fatty infiltration and cirrhosis of the liver based upon the unanticipated hypothalamic injury coincidental to hypophysectomy. Changes in food habits may have led to excessive ingestion of a ration providing unbalanced proportions of the various constituents like those shown to lead to fatty cirrhosis.

After this paper was submitted for publication, Chaikoff, Entenman, Rinehart and Reichert⁴⁸ reported the development of cirrhosis in the livers of dogs deprived of both pituitary and thyroid glands. They found high fat contents in the livers of the animals with hepatic cirrhosis. They did not observe the lesion in dogs that were subjected to thyroidectomy alone. They verified the completeness of hypophysectomy at necropsy, but made no mention of hypothalamic examination.

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DESCRIPTION OF PLATES

PLATE 152

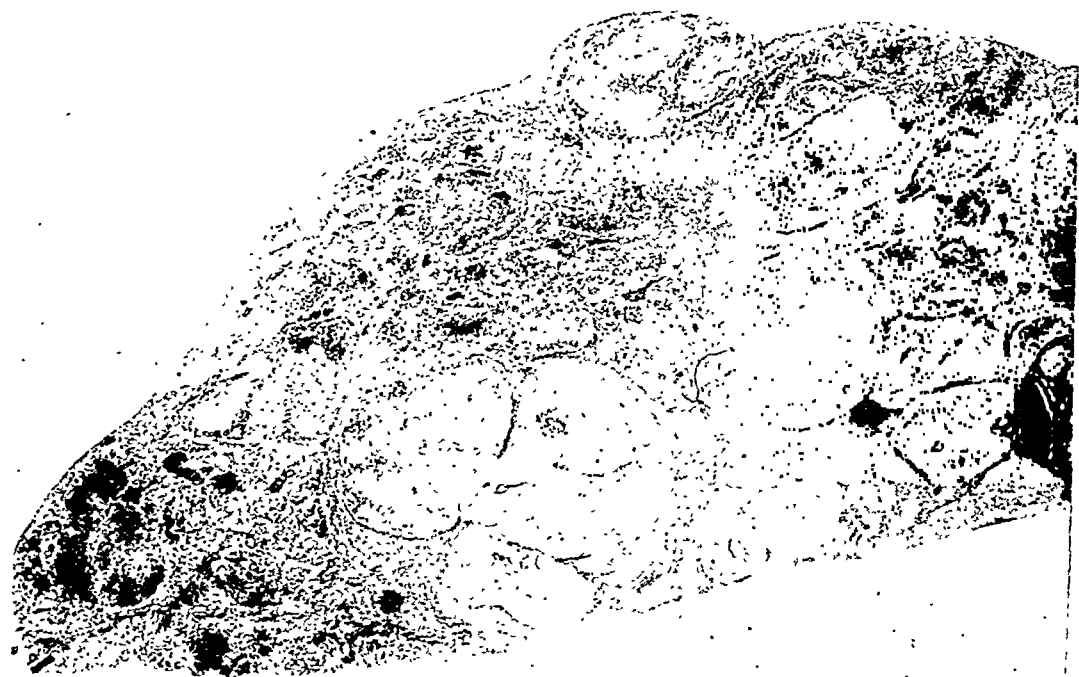
FIG. 1. The nodular appearance of the liver in dog 2.

FIG. 2. Low-power photomicrograph of the liver shown in Figure 1, demonstrating the multilobular deposits of connective tissue. There are numerous hypertrophied areas as well as atrophic zones. (See Fig. 6 for higher magnification.)
 × 10.

1



2



Graef, Negrin and Page

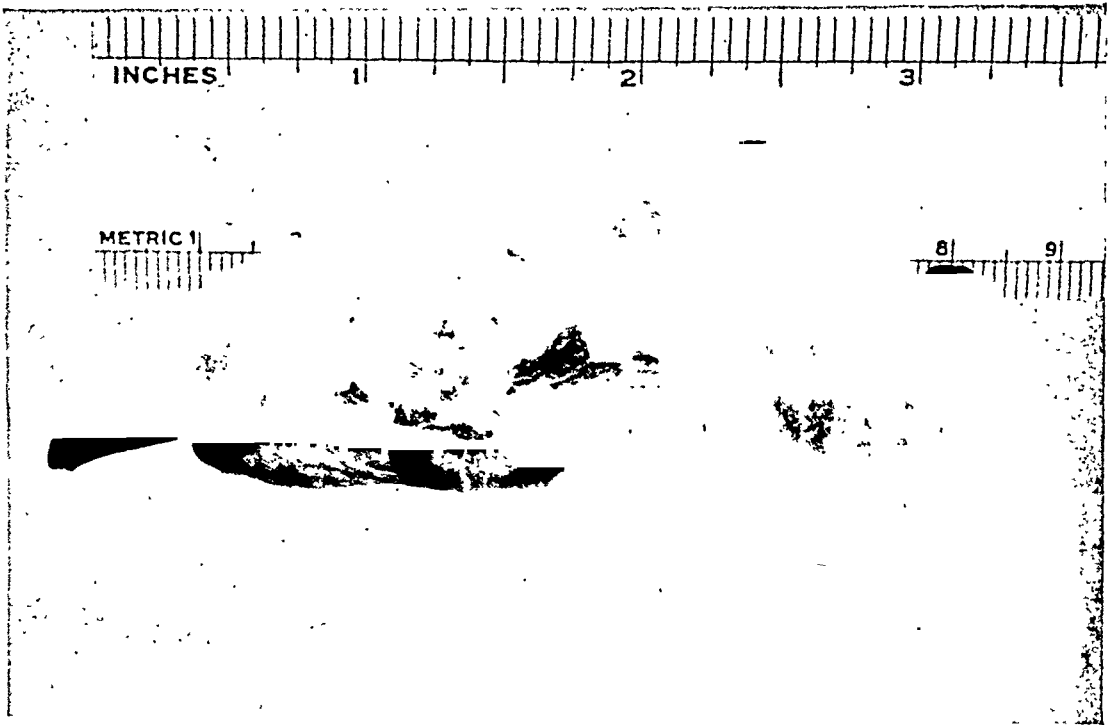
Hepatic Cirrhosis after Hypophysectomy

PLATE 153

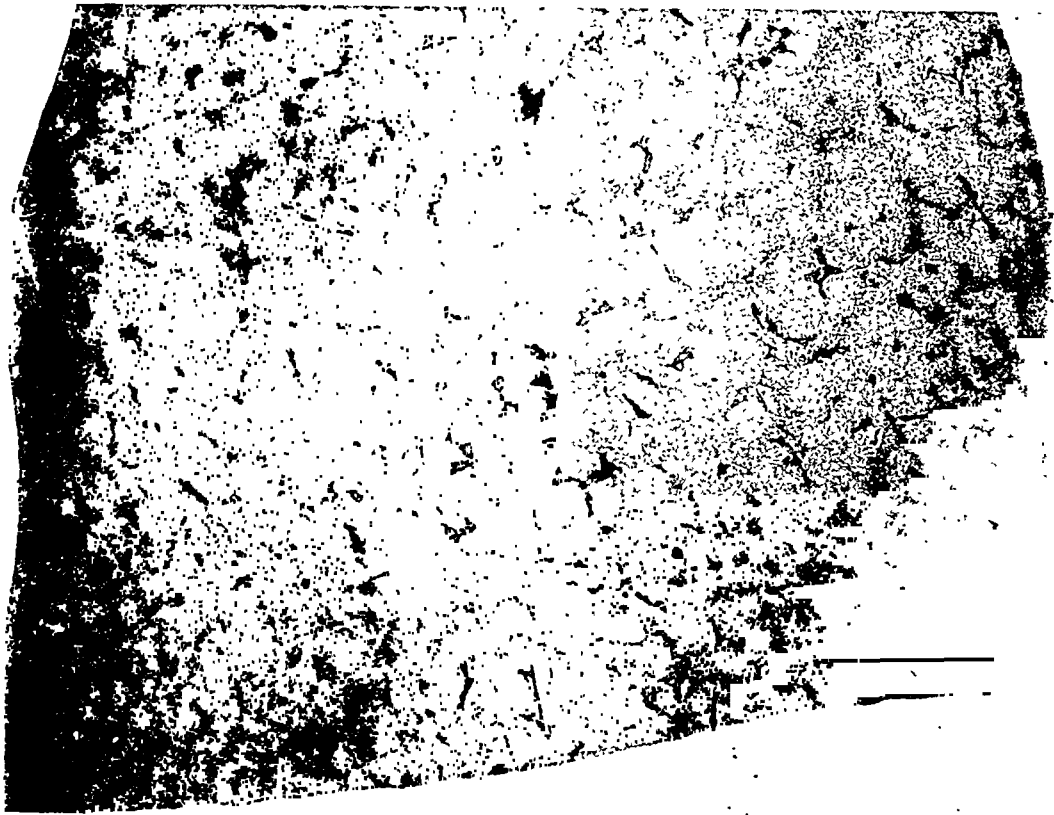
FIG. 3. Photograph of the cut surface of the liver from dog 4, illustrating the prominent appearance of the lobular markings. (See Figs. 4 and 5 for photomicrographs.)

FIG. 4. Low-power photomicrograph of a section of liver shown in Figure 3. The dark areas are prominent portal zones infiltrated with lymphocytes and connective tissue. (See Fig. 5 for higher magnification.) $\times 12$.

3



4



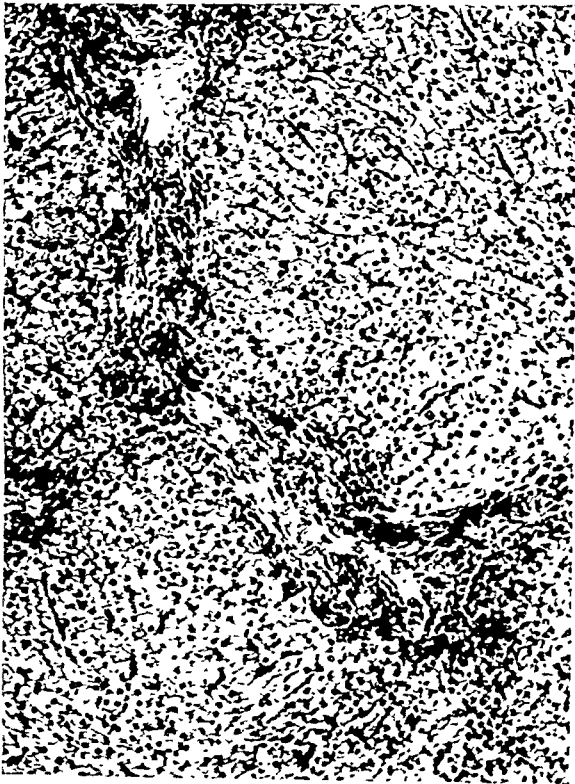
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Hepatic Cirrhosis after Hypophysectomy

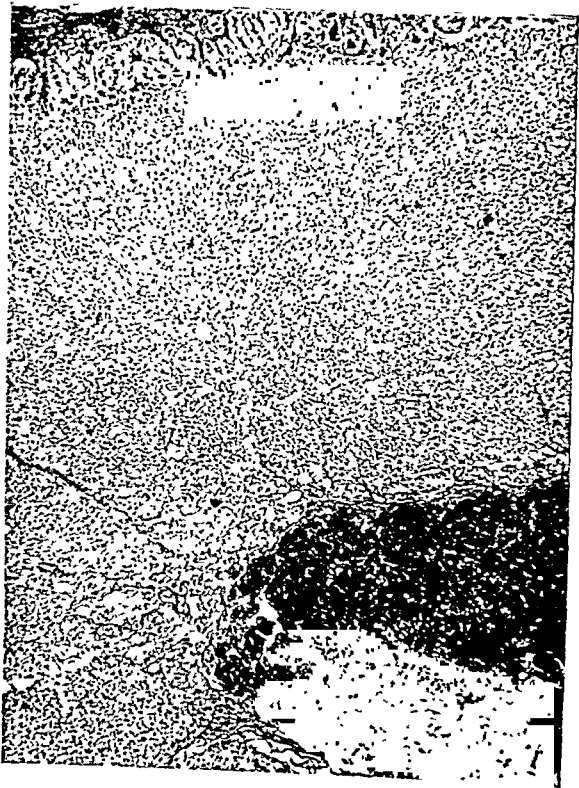
PLATE 154

- FIG. 5. Photomicrograph of a section of the liver of dog 4, showing fatty vacuoles in the hepatic trabeculae. Periportal and perilobular fibrosis are also shown. Hematoxylin and eosin stain. $\times 105$.
- FIG. 6. Section of liver shown in Figure 1 taken through an area of marked fibrosis and atrophy of the liver parenchyma. Some trabeculae show marked fatty vacuolization; others show marked narrowing with widening of the hepatic sinusoids. Hematoxylin and eosin stain. $\times 79$.
- FIG. 7. Section of the adrenal gland from dog 4, showing severe cortical atrophy. The medulla occupies the greater part of the field. The cortico-medullary junction extends along the line from A to A'. Hematoxylin and eosin stain. $\times 52$.
- FIG. 8. Section of the adrenal gland from dog 6. The animal survived hypophysectomy and unilateral adrenalectomy $5\frac{1}{4}$ years. The glomerular zone is intact. The fascicular and reticular zones appear intact although moderately depleted of lipid. Hematoxylin and eosin stain. $\times 52$.

5



7



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PLATE 155

- FIG. 9. Coronal section through hypothalamus of dog 1 at the level of the median eminence, showing rests of pars tuberalis (A) attached to it and a defect of nervous tissue in the medial part of the n. ventro-medialis (B). Hematoxylin and eosin stain. $\times 60$.
- FIG. 10. In this photomicrograph from dog 1, the remnants of the pars tuberalis (A) are seen attached to the median eminence whose lateral part is missing (B). It forms part of a lesion consisting of a defect of the hypothalamus produced presumably when the animal was hypophysectomized $2\frac{1}{2}$ years before death. Hematoxylin and eosin stain. $\times 55$.
- FIG. 11. Coronal section through hypothalamus of dog 2 at the level of the median eminence. The latter is replaced almost completely by connective tissue scar (A) growing from the meningeal membranes (B) covering the inferior part of this portion of the diencephalon. A defect (C) includes the n. periventricularis arcuatus and medial portion of the n. ventro-medialis on both sides; deposits of calcium salts appear as black spots. Hematoxylin and eosin stain. $\times 55$.
- FIG. 12. Sagittal section through hypothalamus of dog 5. On the left can be seen the myelin of the fibers of the optic chiasma (A); on the right side an arrow points to the myelin of the fornix. A defect of nervous tissue is noted between both structures (at B and B') involving the n. ventro-medialis in this photomicrograph. Combined myelin and Nissl stain. $\times 60$.

10



12



B



11



12

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Hepatic Cirrhosis after Hypophysectomy

THE INFLUENCE OF AN ACTIVATED STEROL ON BLOOD PRESSURE IN DOGS *

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Claims of the hypertensive action of vitamin D have appeared persistently in the literature for many years, despite the absence of data that would support such claims. The only support for these claims lies in papers by Appelrot¹ and by Goormaghtigh and Handovsky² showing that in the dog apparently a fair degree of hypertension may be developed in response to vitamin D.

We have previously discussed this problem in some detail and have included data indicating that human subjects have more commonly responded by lowering of systolic blood pressure.³ In no case could it be said that a significant hypertension had occurred.

Recently, Briskin, Stokes, Reed and Mrazek⁴ showed conclusively that no level of administration of vitamin D would produce hypertension in albino rats. Nevertheless, the results on dogs^{1,2} were concise and in spite of numerous earlier failures to produce hypertension in this species by means of vitamin D, it was decided to reopen the problem, using the intra-arterial method of recording pressures. A terminal check under nembutal anesthesia with simultaneous readings on the dial recorder connected with the needle in an artery and on a mercury manometer attached to an arterial cannula showed good agreement between the two methods.

The methods of training have been described previously and no new features of significance were introduced. Preliminary control readings were taken at intervals of 1 to 5 days over a period of 1 month to 6 weeks.

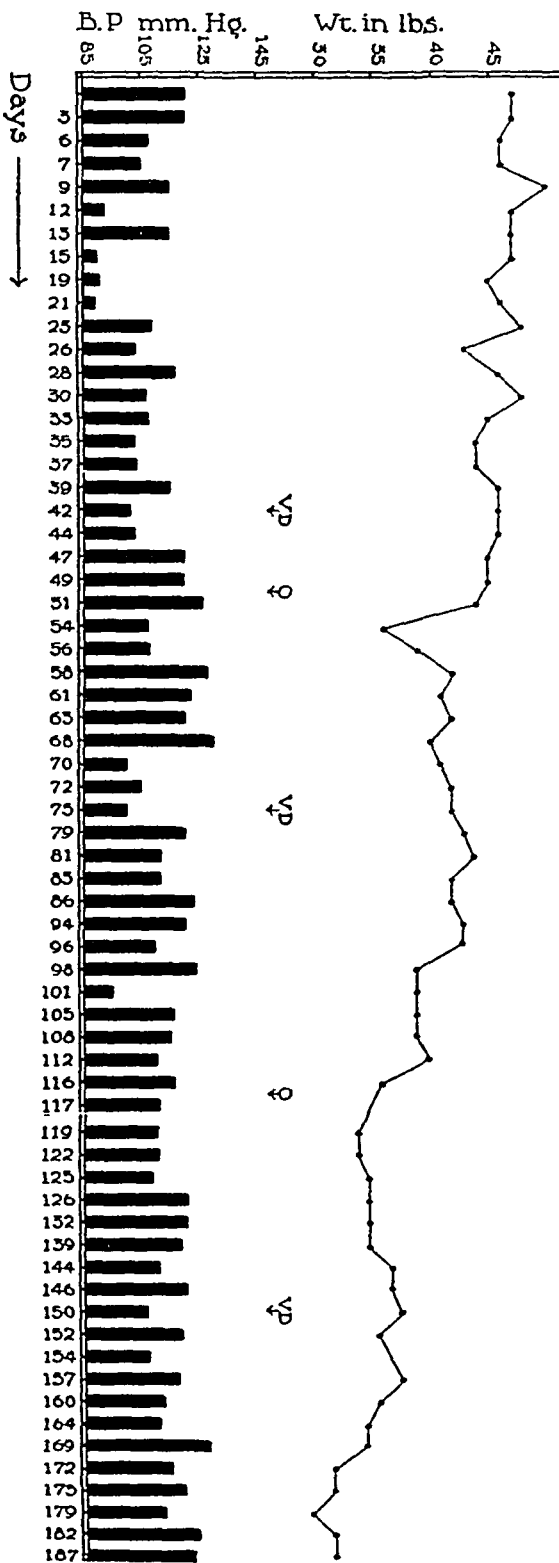
At frequent intervals, sensitivity to adrenalin was tested on 8 dogs in view of the reported observation of increased sensitivity to adrenalin induced by vitamin D.

Twenty dogs were used, 12 being under observation for periods ranging from 108 to 187 days; the other 8 were observed for 38 to 73 days. A protocol is presented in Table I and Text-figure 1. The body weight during the control period of 41 days was maintained at a fairly constant level. With training, the mean arterial pressure was reduced slightly. The average for 19 readings in the entire training period was 106 mm.

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† Department of Pathology.



Text-Fig. 1. Graphic presentation of the data given in Table I.

Hg. Starting with the 42nd day of observation, the dogs received daily 200,000 units of vitamin D as ertron for 8 days, or approximately 10,000 units per kg. per day. With the appearance of anorexia, administration was discontinued. Within the next few days weight declined sharply and was never again recovered completely.

While there were high readings of mean blood pressure following this period, the mean for the entire period of 44 to 75 days inclusive was 114 mm.

At this time a second period of administration was begun and continued through the 116th day, resulting in further weight loss. Except for minor differences, the mean intra-arterial pressure maintained at a slightly lower level. The mean of 12 readings during this period was again 114 mm.

After a rest period, administration of the vitamin was resumed on the 150th day and continued through the 172nd day. The mean of seven readings was 116 mm., and for four subsequent readings, 118 mm. In view of the large variations it cannot be considered that the progressively ascending mean for each successive period represents hypertension.

In all of the animals isolated, extremely high readings occurred in both control and experimental periods, as well as occasional extremely low ones. These could seldom be correlated with any demonstrable change in the animal's condition or environment. In fact, the same animal might progress from one extreme to the other between two different readings made on the same day, although there was seldom any pronounced change observable during the time that the needle was in place, except for a slight decrease after the initial puncture was made.

The extensive utilization of this method of testing blood pressure in intact dogs in this department in recent years has produced sufficient data to justify the conclusion that all of the fluctuations observed in this study are within the physiological range (Wakerlin).⁵

Furthermore, the upward trend observed in this particular animal was reversed in five others (Table I). In the remainder there was practically an even mean pressure throughout. The tendency for blood pressure in rats to follow weight changes (Briskin and co-workers⁴) is not in evidence in the dogs of this series. This suggests that the two species possess different mechanisms of circulatory response to weight changes. In this respect the dog behaves more nearly like man.

The results of adrenalin tests likewise failed to confirm the claims of Goormaghtigh and Handovsky² that vitamin D sensitizes animals to this agent. In Text-figure 2 are shown two sets of graphs of eight adrenalin tests, the lower four during a period when no vitamin was given, the upper four during a period of daily administration of 200,000 units. Graphs for the adrenalin tests on the other dogs showed just as little difference as in this illustration. It is apparent, then, that vitamin D does not sensitize dogs to adrenalin. The standard dose of 1.5 gamma per kg. was established by preliminary trial as an approximate threshold dose, since it seemed probable that any sensitization would be more readily apparent at a moderate level.

Just as this manuscript was being prepared, Katz, Rodbard and Meyer⁶ published a report of the administration of vitamin D₂ in propylene glycol to 10 dogs, 5 of which were experimental renal hypertensive animals, 3 were spontaneously hypertensive and 2 were normotensive. Subcutaneous injections of 40,000 units per day for 31 days to the 3 spontaneous hypertensive dogs and oral administration of 400,000 units per day to the others produced no evidence of hypertensive response except in 3 animals. In 1 normotensive dog with denervation of the carotid sinus there was mean elevation by 24 mm. Hg systolic/16 mm. Hg diastolic during 15 days, which disappeared thereafter. A similar reaction occurred in 1 spontaneous hypertensive dog with a

TABLE I
Sample Protocol for 1 of the 20 Dogs Used

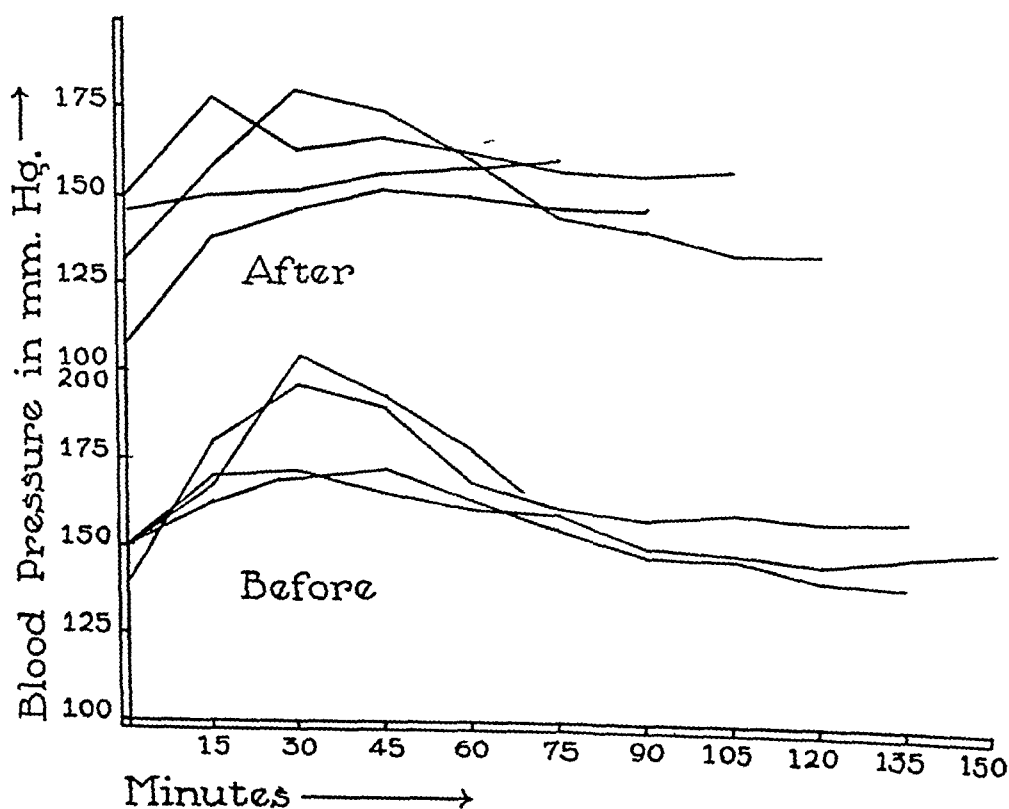
Days	Mean arterial pressure	Weight	Experimental procedure
	<i>mm.Hg</i>	<i>lbs.</i>	
	119	47	Control
3	119	47	
6	107	46	
7	105	46	
9	116	50	
12	93	47	
13	115	47	
15	90	47	
19	91	45	
21	90	46	
23	109	48	
26	103	43	
28	117	46	
30	107	48	
33	108	45	
35	102	44	
37	103	44	
39	109	46	
42	101	46	200,000 units of vitamin D
43			200,000 units of vitamin D
44	103	46	200,000 units of vitamin D
45		45	200,000 units of vitamin D
46			200,000 units of vitamin D
47	119	45	200,000 units of vitamin D
48		42	200,000 units of vitamin D
49	119	45	200,000 units of vitamin D
50			(anorexia)
51	126	44	(anorexia)
54	107	36	
56	108	39	
58	128	42	
61	122	41	
63	120	42	
68	130	40	
70	100	41	
72	105	42	
75	100	42	200,000 units, ertron
76	100,000 units daily through 108th day
79	119	43	<i>vide supra</i>
81	111	44	<i>vide supra</i>
83	112	42	<i>vide supra</i>
86	123	42	<i>vide supra</i>
94	119	43	
96	111	43	
98	124	39	<i>vide supra</i> (toxic)
101	95	39	<i>vide supra</i>
105	116	39	<i>vide supra</i>
108	115	39	<i>vide supra</i>
111	300,000 units
112	110	40	200,000 units
116	116	36	200,000 units
117	111	..	(anorexia)
119	111	34	(anorexia)
122	111	34	(anorexia)
125	109	35	Adrenalin test
126	121	35	Adrenalin test
132	121	35	
139	119	35	
144	111	37	Adrenalin test
146	121	37	Adrenalin test

TABLE 1 (continued)
Sample Protocol for 1 of the 20 Dogs Used

Days	Mean arterial pressure	Weight	Experimental procedure
	<i>mm. Hg</i>	<i>lbs.</i>	
150	107	38	100,000 units, ertron, daily through 168th day
152	119	36	<i>vide supra</i>
154	107	..	<i>vide supra</i>
157	118	38	<i>vide supra</i>
160	113	36	<i>vide supra</i>
164	111	35	<i>vide supra</i>
169	129	35	200,000 units daily
172	116	32	300,000 units daily
175	119	32	<i>vide supra</i>
179	113	30	Adrenalin test
182	121	32	<i>vide supra</i>
187	119	32	Adrenalin test

mean elevation of 19/18 mm. In 1 renal hypertensive animal a mean increase of 26/27 mm. was attained, and during the succeeding 15 days after administration the mean elevation was 27/35 mm.

The interpretation of these results would appear to us to depend on individual opinion, since neither the actual levels, the individual readings, nor the standard deviations were given. In our experience, if control observations are continued long enough, fully as large variations may occur in the control periods.



Text-Fig. 2. Adrenalin tests before and after the administration of activated sterol.

Another criticism lies in the failure to grade the dosage of vitamin D according to body weight. If this were done, it is not apparent from the report. However, the ultimate conclusion of these authors is that vitamin D has only a slight and irregular tendency to produce hypertension in dogs.

One might raise the question as to whether the differences are related to the particular preparation of vitamin D. This seems unlikely as there is, at present, no suggestion of evidence that any vehicle for this vitamin has hypertensive action, either alone or in combination with the vitamin. We have quite generally found ertron less toxic than other forms of vitamin D. The fact that ertron produced toxication but did not produce significant hypertension strongly suggests that hypertension is not a fundamental part of the syndrome of toxication by vitamin D in the rat, dog, or man. Katz, Rodbard and Meyer⁶ supported that thesis for the dog. At present there is no evidence that ertron is less hypertensive than other forms of vitamin D merely because it is slightly less toxic. We have some evidence that the active material in ertron is not calciferol, while that used by Katz, Rodbard and Meyer is crystalline calciferol dissolved in propylene glycol. On the basis of present information there is no reason to assume that the chemical differences among the numerous vitamers D are of sufficient physiological significance to account for the apparent differences among the published reports.

Also, the form of vitamin used in this investigation produced weight loss and anorexia in some cases at levels as low as 5000 units per kg. per day. In every case the evidence indicates that the condition was true toxication by vitamin D since all animals recovered when administration was discontinued. When administration was continued uninterruptedly, the animals invariably died without developing hypertension. Therefore, it may be assumed that hypertension is not a part of the symptom complex of vitamin D-toxicity. Since it has occurred in the experience of others, it must have been due to some other factor or factors not apparent in the published reports and not measurable in terms of antirachitic potency. Also, it may be pointed out that Katz, Rodbard and Meyer⁶ did not continue their observations as long as in this investigation.

Our previous attempts to demonstrate the development of hypertension in dogs with viosterol, crystalline calciferol, calciferol in propylene glycol and vitamin D₃ have proved unsuccessful as in the experiments reported here.

It should be stressed again that our experiments were of the following types: (1) long-term, moderate dosage; (2) very large individual

doses; (3) long-term, low dosage; (4) short-term, high dosage. Quantitatively and qualitatively the results were homogeneous among these types of experiments.

In an earlier experiment 1 dog was observed for 18 months after a period of toxicity in which the weight loss amounted to 50 per cent. The animal was estimated to be 8 years old. With the additional period of observation he was 9½ years old when the final blood pressure test was made. This should be comparable to 60 years or more in man; yet no hypertension was present, although some kidney damage was found.

TABLE II
Degree of Renal Arteriolar Hypertrophy as Related to Other Experimental Data

Dog no.	Weight	Mean blood pressure			Degree of medial hypertrophy in kidney	Vitamin D units		
		Before	After	Change		Total dose	Total per kg.	Dose per kg. per day
	kg.	mm.Hg	mm.Hg	mm.Hg				
11	12.7	116	114	- 2	+++	3,835,000	301,960	9,150
12	13.2	134	147	+13	+	6,030,000	456,820	13,052
13	14	134	135	+ 1	++	4,575,000	326,786	27,232
14	11.3	91	111	+20	++	4,245,000	375,664	13,416
35	11	131	125	-14	++	1,705,000	144,492	10,320
61	16.3	114	114	0	++	3,810,000	233,742	19,478
62	14.5	122	122	0	+	3,230,000	222,758	13,922
69	15.5	117	131	+14	+++	3,450,000	222,580	5,429

Tissues were removed from the last 8 dogs of the series for histopathological examination. In the myocardial arterioles there was occasionally seen a mild degree of medial hypertrophy. A similar change was seen less frequently in the arterioles of the spleen. It was only in the sections of the kidneys that any marked changes were found, in the form of varying degrees of arteriolar medial hypertrophy, cuneate areas of fibrosis, and lymphocytic infiltration. Since it seems probable that only the first of these changes is of possible significance in relation to blood pressure, further discussion will be confined thereto. A condensed arrangement of the data is presented in Table II.

The degree of pathological change is somewhat arbitrarily designated as 1 plus (+), 2 plus (++), or 3 plus (+++), the first representing the mildest state at which definite changes could be detected, the latter the most extreme degrees, approaching complete obliteration of the lumina. The question of the statistical significance of the changes in blood pressure has already been discussed. Nevertheless, the means of the pre-treatment and treatment periods show that there was a marked increase in 3 dogs, a marked decrease in 1, with no marked change in the other 4.

Rearrangement of the data in ascending order for each of the factors in Table II resulted in a wholly random distribution and complete failure to demonstrate a close correlation between the degree of the vascular lesion and any one of the factors in the other columns. Nevertheless, it is a fact that all of the dogs did show pathological changes in the renal arterioles and all of them received vitamin D.

The dog receiving the highest total dose, no. 12, showed only a first degree change, while dogs 11 and 69 showed third degree changes on moderate total doses, but low daily doses per kg. Paradoxically, dog 35 showed second degree changes with the lowest total dose.

Only 1 of the 3 dogs with high mean pressure after treatment showed third degree changes in the arterioles.

CONCLUSION

In a series of 20 dogs receiving doses of vitamin D of sufficient potency to produce toxicity manifested by anorexia and weight loss, blood pressure determinations by the intra-arterial needle method showed that hypertension had not been produced. Also standardized adrenalin tests showed that none of the dogs had developed sensitivity to this drug.

Microscopical examination of the kidneys of 8 of these dogs showed varying degrees of medial hypertrophy in the renal arterioles of all of them, but there was no close correlation between dosage, blood pressure changes and the degree of pathological change.

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FEMINIZATION IN MALE DOGS

A SYNDROME ASSOCIATED WITH CARCINOMA OF THE TESTIS AND MIMICKED BY THE ADMINISTRATION OF ESTROGENS *

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In human pathology several syndromes occurring with neoplasms of endocrine glands are well recognized. The coincidence of symptom-complexes and endocrine tumors in animals commonly employed experimentally not only offers an opportunity for the investigation of the pathologic alterations in the observed animal, but also affords some insight into similar diseases in man.

A review of the literature on canine neoplasms disclosed 6 cases of carcinoma of the testis with which a characteristic group of symptoms and signs were associated. When these cases were analyzed in relation to recent experiments in which diethylstilbestrol was administered to male dogs, the similarity of several findings in the experimental animals to the features of the clinicopathologic picture seen with carcinoma of the canine testis became evident. The clinical and pathologic details of these 6 cases of carcinoma of the testis, and the changes evoked in male dogs by the administration of natural and synthetic estrogens in the experience of other workers, will be compared and discussed together with recent experiments in which diethylstilbestrol was fed to male dogs.

SUMMARY OF 6 CASES OF CARCINOMA OF THE TESTIS FROM THE LITERATURE

In 1908, Wooldridge¹ described an aged black Pomeranian dog weighing 16 lbs., which for 1 year had experienced gradual enlargement of the right testis and simultaneous loss of hair which involved progressively the neck, abdomen, back and legs. During life the dog licked the enlarged right testicle and, in the words of the owner, "was pleased when we gave it a gentle rubbing." Two photographs illustrated the enlarged right testis and the general lack of hair. Also suggested in them was the prominence of the penile sheath and mammary glands. At autopsy the right testicle revealed a 17 oz. tumor, diagnosed as carcinoma by Sir John McFadyean. No other lesions were found in the well nourished cadaver, although specific statements about the condition of the opposite testis, the other endocrine glands, or the secondary sex glands were not made.

* Received for publication, December 10, 1943.

Testicular tumors associated with mammary, prostatic and other changes in 3 cryptorchid dogs were reported by Greulich and Burford.² The first dog was a Boston terrier, 4 years of age, which attracted other male dogs like a bitch in heat. The undescended right testis at the caudal pole of the right kidney was occupied by a tumor measuring 48 by 40 by 24 mm., variously diagnosed as a seminoma, an embryoma, and an adenocarcinoma. The right gubernaculum testis extended to the internal inguinal ring. The left testis in the scrotum revealed spermatogenesis arrested at the secondary spermatocyte stage and interstitial fibrosis. The prostate showed metaplasia of the epithelium of ducts and acini to a stratified squamous type. The epithelium in the right ductus deferens was lower than that in the left. Also noted were several "adenomas" in the reticular layer of the adrenal cortex, a possible slight excess of eosinophilic cells in the pars anterior of the hypophysis and some hyperplasia of the ducts and acini of the breasts.

The second dog was a wire-haired fox terrier about 2 years old and sexually attractive to males. At operation a tumor in the right upper quadrant of the abdominal cavity was found to occupy the right testis. It weighed 538.6 gm., measured 125 by 94 by 72 mm., and extended into the left upper quadrant. The histologic structure of this neoplasm was similar to that of the tumor in the first dog. Following operation, the dog lost his sexual attractiveness to other males and died 9 weeks later of generalized peritonitis. Caudal to the right adrenal was an 18 mm. tumor, in structure like the one removed surgically. The left testis in the scrotum showed arrest of spermatogenesis at the spermatogonial stage. The prostate resembled that of a newborn or young dog. The ductus deferentes were intact. Hyperplasia of the cortex and medulla of the right adrenal, some hyperplasia of the ducts and acini of the breasts, and an apparent excess of acidophils in the anterior lobe of the hypophysis were also found.

No estrogenic activity of the tumors in these 2 dogs was demonstrated. The photographs of these 2 animals suggested swelling of the penile sheaths with enlargement of the prepuce as well as relatively conspicuous breasts.

The third dog was a fox terrier, 10 years of age, and bilaterally cryptorchid since birth. For 2 years a swelling had been noticed in the left inguinal region. The histologic structure of the left testicular tumor was similar to that of the neoplasms in the first and second dogs. The right testis in the inguinal canal showed tubules lined by a single layer of spermatogonia and surrounded by fibrous stroma. The prostate was enlarged to three times normal size and disclosed stratified squamous epithelial metaplasia of the ducts and acini. The adrenals

were normal, but the breasts were involved by cystic hyperplasia of the ducts and acini.

Although most pronounced in the third dog, loss of hair and increased pigmentation of the skin over the ventral and ventrolateral surfaces of the abdomen were found in all 3 animals. From a study of the testicular neoplasms in them as reflected in the photomicrographs,² the opinion has been formed³ that these were actually adenocarcinomas, in which the spermatogonia, primary spermatocytes, and probably the sustentacular or Sertoli cells lining the seminiferous tubules undergo proliferation and palisading in an atypical glandular pattern with persistence and stretching of many of the intertubular septa.

A terrier, 7½ years of age, case 1 described by Zuckerman and Groome,⁴ had been regarded by his owner as normal until the age of 6 years, except that the animal had "never been known to pursue bitches." For 18 months, the dog had apparently been regarded as a female dog in perpetual heat by the other dogs in the neighborhood. In the last few months increasing drowsiness and enlargement of the nipples had been noted. At necropsy,⁴ the testes were stated to be small and in an atrophic condition with spermatogenesis probably in abeyance or much slowed down, although fixation of the tissue was imperfect. In a later communication,³ it was stated that this same dog had an adenocarcinoma of the testis. Additional autopsy findings⁴ included an enlarged prostate with extensive metaplasia to stratified squamous epithelium, a swollen penile sheath and four pairs of enlarged abdominal nipples. In the photograph depicting these last two changes, thinning and loss of hair from the ventral abdominal wall were strongly suggested.

A fox terrier, 12 years old, case 11 of Zuckerman and McKeown,³ had had for 6 months an enlarged and inflamed scrotum, irregular pigmentation of the skin of the trunk in black patches and increased prominence of the penile sheath and nipples. The swollen right testis showed a large hydrocele and an adenocarcinoma with necrotic metastases in the liver and spleen. The left testis was small. The prostate was enlarged and affected by stratified squamous epithelial metaplasia. Three other dogs, cases 222, 227, 242, described in the same paper, had adenocarcinoma of the testis and stratified squamous epithelial metaplasia of the prostate, although clinical details were not listed. The first dog was a Dalmatian, 15 years of age; the second, a mongrel, was 8 years old; and the third, an Alsatian, was 11 years of age. Another dog, case 225, a fox terrier, 6 years old, was afflicted with an adenocarcinoma of the testis and a carcinoma of the prostate (type not

stated), the two lesions being regarded as occurring together by chance. If the type of carcinoma in the prostate of this dog were actually squamous-celled, the stimulation of the prostate to anaplastic change by the endocrine action of the adenocarcinoma of the testis might be comparable to the formation of adenocarcinoma of the uterine fundus through estrogenic stimulation, as seen in some women with a pre-existing granulosa cell tumor of the ovary. That the presence of adenocarcinoma of the testis in the 15 dogs examined for this lesion by these authors was not associated with any constant changes in the prostate was demonstrated by the histologic diagnosis on the remaining nine prostates, of which four showed great involution of the glandular system; three were normal; and two were much reduced in size.

EXPERIMENTAL OBSERVATIONS FROM THE LITERATURE

The histologic findings in the prostates of 5 puppies (2 normal and 3 castrated) injected with varying amounts of estrone were described by Zuckerman and Groome,⁴ who received the tissues from deJongh and Kok.⁵ The structures involved included the urethral epithelium, the collecting tubules, the glandular acini and the uterus masculinus. The essential changes consisted of arrest of secretion, epithelial hyperplasia, and epithelial metaplasia. The last two processes graded into each other to result in the conversion of the once single layer of columnar cells into a heavily stratified and desquamating epithelium. The glandular system was transformed into a series of cysts filled with shed epithelial cells and separated from each other by fibrous trabeculae covered on each side by flattened epithelial cells.

Arnold, Hamperl, Holtz, Junkmann and Marx,⁶ employing estradiol benzoate and estradiol monobenzoate, described similar changes, including abscesses, in the prostates of 7 adult male dogs, the testes of which showed aspermatogenesis and disappearance of the germinal epithelium.

Huggins and Clark⁷ treated 8 male dogs (3 puppies, 3 castrated adults, and 2 adults with cystic hyperplasia of the prostate) with diethylstilbestrol and observed the same changes in the prostate as had Zuckerman and Groome⁴ in the material of deJongh and Kok.⁵

Failure of regeneration and loss of hair were reported by Gardner and DeVita⁸ in 4 male dogs which received estradiol benzoate beginning in puppyhood. This phenomenon was also observed in 4 adult male dogs fed diethylstilbestrol.⁹ The animals described in that communication⁹ are the subjects of the following protocols, in which, for the sake of completeness, the data on dosage will be incorporated.

PROTOCOLS OF EXPERIMENTS

The first dog, a white and black fox-terrier mongrel, about $1\frac{1}{2}$ years of age, weighing $15\frac{1}{2}$ lbs. and having short hair, received 330 mg. of diethylstilbestrol (stilbestrol) in 20 doses of 5 mg., 19 of 10 mg., and 2 of 20 mg., over a period of 129 days. On the 172nd day, the animal was sacrificed.

The second dog, a white and black cocker-spaniel mongrel, about 3 years old, weighing 18 lbs. and having hair of medium length, received 1790 mg. of stilbestrol in 20 doses of 5 mg. and 169 of 10 mg. in a period of 292 days. Five hundred milligrams of stilbestrol were then implanted subfascially in the right upper quadrant of the ventral abdominal wall. On the 322nd day the animal weighed 17 lbs., was extremely toxic, and was sacrificed.

The third dog, a black water-spaniel mongrel, about $1\frac{1}{2}$ years of age, weighing $17\frac{1}{2}$ lbs. and having long hair, received 1850 mg. of stilbestrol in 185 doses of 10 mg. in a period of 280 days. On the 280th day his weight was 20 lbs., and 500 mg. of stilbestrol were implanted subfascially in the right upper quadrant of the ventral abdominal wall. On the 294th day increased hair loss (Figs. 3 and 5) and depression of libido were prominent symptoms. Further clinical details will be given for this animal, which is still alive and well.

The fourth dog, a black and white collie-scottie mongrel, about 4 years old, weighing about 27 lbs. and having long hair, received 2985 mg. of stilbestrol in 100 doses of 10 mg., 6 of 15 mg., 6 of 20 mg., and 71 of 25 mg. in a period of 291 days. On the 291st day he weighed 24 lbs., and 500 mg. of stilbestrol were implanted subfascially in the right upper quadrant of the ventral abdominal wall. Between the 298th and 305th days, dysuria, hematuria, oliguria, and finally anuria developed. On the 305th day, the animal was sacrificed.

RESULTS

The general thinning of the hair; the loss of hair from the perineum, penile sheath, thighs, buttocks, scapular regions, and circumocular areas (Fig. 1) and from the ventral surfaces of the tail, abdomen, thorax and neck; and the failure of regeneration of hair at areas on the forelegs clipped for venipuncture (Fig. 1) have been described.⁹ Libido, which was tested by placing each animal with frequently available female dogs in estrum, was little affected or possibly increased until the 500 mg. dosage level of stilbestrol was exceeded. At the height of medication in the animals receiving more than this amount

of the drug, the libido was definitely greatly depressed, the breasts showed increased prominence, the penile sheath became swollen, the prepuce enlarged and the testes were reduced in size. In the fourth dog the prepuce was superficially ulcerated (Fig. 2).

The tissues from the first, second and fourth dogs were fixed in Zenker's fluid, blocked in paraffin, cut at 6 μ , and stained with hematoxylin and eosin. Those organs usually investigated at a reasonably complete necropsy were examined, but only the alterations observed in the testes, prostate, vasa efferentia, epididymal ducts, ductuli efferentes, penile sheath, breasts, skin, thyroid and adrenals will be described.

Testes. In the first dog the seminiferous tubules were small and spaced relatively far apart. Spermatogenesis in most tubules was arrested at the spermatid stage, although a few small clumps of spermatozoa occupied the lumina of a few tubules. In the second dog the seminiferous tubules were greatly shrunken, the seminal epithelium was developed through the primary spermatocyte stage, and the connective tissue in the stroma was relatively increased. In the fourth dog the seminiferous tubules were very small, most tubules were lined by a layer of spermatogonia, the remaining tubules were replaced by connective tissue and the stroma exhibited increased connective tissue.

Prostate. In the first dog the urethra showed metaplasia to stratified squamous epithelium, the dilated ducts were lined by flattened epithelium, the acinar epithelium was low cuboidal or columnar, and the interacinar stroma was arranged in slender strands. In the second dog stratified squamous epithelial metaplasia involved the urethra, ducts and acini, with sloughing of cornified cells; some masses of necrotic epithelium were seen; and the stroma was diffusely infiltrated by chronic inflammatory cells. In the fourth dog were found extensive epithelial metaplasia of the urethra, ducts and acini to a stratified squamous type; multiple abscesses, and obstruction of the urethra by a conglomerate abscess with hypertrophy of the urinary bladder; sub-acute cystitis, and chronic pyelonephritis.

Vasa Efferentia, Epididymal Ducts, and Ductuli Efferentes. In the first, second and fourth dogs the epithelial cells lining the vasa efferentia, epididymal ducts, and ductuli efferentes were reduced in height and volume, and frequently showed hyaline transformation of the cytoplasm. The glandular recesses of the ampullae of the vasa efferentia displayed similar changes.

Penile Sheath. In the second and fourth dogs, the epithelial lining of the penile sheath showed intercellular edema, great thickening and hypercornification, characteristics noted ¹⁰ in the vaginal epithelium of

female dogs in proestrus. The prepuce of the second dog revealed changes like those to be described for the skin. The epidermis of the prepuce in the fourth dog was largely ulcerated and replaced by proliferating granulation tissue. The epithelium of the surviving epidermis and of the hair follicles showed thickening, intercellular edema and increased granularity of the stratum granulosum. The sebaceous glands were moderately enlarged and scattered sweat glands were dilated and lined by flattened epithelium.

Breasts. In the second dog the epithelial lining cells of the ducts and of a few acini had proliferated and the periductal connective tissue was increased. In the fourth dog the epithelium lining the ducts and acini was hyperplastic, some ducts and acini were dilated and lined by flattened epithelium and the cytoplasm of some acinar cells was hyalinized.

Skin. In the second dog the epidermis was intact. The epithelium of the hair follicles was thinned, the inner follicular cells showed hyaline cytoplasm and the hair follicles were shrunken. Most sebaceous glands revealed disappearance of the lipid-laden cells, shriveling of the epithelium and shrinkage. Many sweat glands were dilated and lined by flattened epithelium. In the fourth dog the epidermis was intact. Also observed were thinning of the epithelium of the hair follicles, hyaline cytoplasm in the inner follicular cells and shrunken hair follicles. About half the sebaceous glands revealed absent lipid cells and shriveled epithelium. The other half showed moderate increase in size and well filled lipid cells. Scattered sweat glands were dilated and lined by flattened epithelium.

Thyroid. In the second and fourth dogs the follicular epithelial cells exhibited shrinkage of the cytoplasm and condensation of the nuclear chromatin. In many follicles, reduced in size, the colloid was scanty or lost.

Adrenals. In the glomerular and fascicular cells of the cortex of the first, second and fourth dogs the cytoplasm was shrunken and the nuclear chromatin was condensed. Cytoplasmic lipid was lost from the fascicular cells as demonstrated by the scharlach R stain on frozen sections of formaldehyde-fixed material.

After the 280th day the third dog received no stilbestrol. On the 396th day he weighed 21 lbs., the hair was almost completely regenerated in the areas from which it had been lost, the swelling of the breasts and penile sheath had subsided and libido had returned as evinced by copulation with female dogs in estrus. On the 583rd day he was generally active, hair was abundant (Figs. 4 and 6), libido persisted and the size of the testes was about normal.

COMMENT

In my analysis of the data upon 6 dogs with carcinoma of the testis (3 in cryptorchid testes and 3 in scrotal testes) from the literature, the following observations indicating a definite syndrome were evident: (1) adenocarcinoma as the type of neoplasm found and defined by Zuckerman and McKeown;³ (2) varying degrees of atrophy of the seminiferous epithelium of the opposite testis (one cryptorchid); (3) metaplasia to stratified squamous epithelium in the prostatic urethra, ducts and acini with hypertrophy of the prostate; (4) hyperplasia of the ducts and acini of the breasts with mammary enlargement; (5) swelling of the penile sheath; (6) loss of hair; (7) attraction of other male dogs like a female dog in estrum; and (8) depression of libido. The increased pigmentation of the skin might possibly be included in the syndrome except that patches of pigmentation in the skin of normal dogs are common enough in the experience of investigators who have had occasion to shave the trunks of dogs. The breeds of the 6 animals were Pomeranian, Boston terrier, wire-haired fox terrier (2), fox terrier and terrier. Their ages were "advanced," 4, about 2, 10, 7½ and 12 years.

From the experimental observations in the literature on the effects of estrogens in male dogs and from the findings in the 4 dogs described, the points of similarity to the symptom-complex of feminization associated with carcinoma of the testis become apparent in the following: (1) aspermatogenesis and varying degrees of atrophy of the germinal epithelium of the testes with fibrosis of the stroma; (2) metaplasia to stratified squamous epithelium in the prostatic urethra, ducts and acini with hypertrophy of the prostate; (3) hyperplasia of the ducts and acini of the breasts with mammary enlargement; (4) swelling of the penile sheath; (5) loss of hair; and (6) depression of libido.

In the present experiments the following changes were attributed to the action of the stilbestrol: (1) atrophy of the epithelium lining the vasa efferentia and the glandular recesses of their ampullae, the epididymal ducts and the ductuli efferentes; (2) hyperplasia of the lining epithelium of the penile sheath; (3) partial atrophy of the hair follicles and sebaceous glands of the skin; and (4) partial atrophy of the thyroid gland and adrenal cortex. Evident in the third dog was the recoverability from the hair loss, the depression of libido, the swelling of the breasts and penile sheath and the reduction of the size of the testes.

SUMMARY

A syndrome of feminization in male dogs associated with carcinoma of the testis includes the following features: (1) adenocarcinoma as the type of neoplasm; (2) varying degrees of atrophy of the opposite

testis; (3) stratified squamous epithelial metaplasia of the prostatic urethra, ducts and acini with hypertrophy of the prostate; (4) hyperplasia of the ducts and acini of the breasts with mammary enlargement; (5) swelling of the penile sheath; (6) loss of hair; (7) attraction of other male dogs like a female dog in estrum; and (8) depression of libido. The similarity of the changes produced by both natural and synthetic estrogens to several features of this symptom-complex suggests that the carcinoma of the testis elaborates estrogenic material or at least a substance altered in some metabolic process to a compound having a feminizing action.

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[Illustrations follow]

DESCRIPTION OF PLATE

PLATE 156

- FIG. 1. Fourth dog, 232nd day. Hair loss from circumocular areas. Failure of regeneration of hair on forelegs.
- FIG. 2. Fourth dog, 305th day. Hair loss from ventral abdominal wall. Swelling of penile sheath and ulcerated prepuce. Prominent breasts at right costal margin in upper left corner and to left of penis.
- FIG. 3. Third dog, 294th day, rear view. Hair loss from buttocks, perineum, legs and ventral surface of tail.
- FIG. 4. Third dog, 583rd day, rear view. Regeneration of hair on tail in upper part of figure; and on perineum, buttocks, and legs in lower part.
- FIG. 5. Third dog, 294th day. Loss of hair from ventral surfaces of thorax and abdominal wall. Prominence of penile sheath and breasts.
- FIG. 6. Third dog, 583rd day, close-up of ventral abdominal wall. Regeneration of hair. Hind legs at bottom of figure.



Mulligan

Feminization in Male Dogs

MULTIPLE DIFFUSE FIBROSARCOMA OF BONE *

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In 1936 I encountered a malignant tumor of the skeleton which defied classification. The case was submitted to the Bone Sarcoma Registry of the American College of Surgeons where it stands recorded (no. 2032) as unique. A number of experienced American and European bone pathologists who studied the tumor expressed interesting views, some of which will be given; none had seen a similar tumor. Because it presents several features which are new for bone tumors, it is reported at this time.

Histologically the tumor was a fairly innocent-appearing, long spindle-celled fibrosarcoma of not uncommon appearance. The unusual features consisted of the manner of its growth and of its distribution in the skeleton in association with this histological type. It was widely distributed in bones, which it destroyed. Its disposition was essentially that of the reticulo-endothelial and hemopoietic tissues in the bone marrow of adults. Nowhere did it form any considerable mass or enlargement suggestive of a primary site of origin. There were small metastases in the viscera.

While tumors with this distribution and behavior are not rare, being characteristic of the myelomas, the association of these features with the cytology encountered in this case is unusual.

REPORT OF CASE

L. D., white, male, 43 years old, who was employed as a coal passer on a railroad, was a patient of Dr. L. H. Sloan † at the Illinois Central Hospital, Chicago. Except for dryness and scaling of the skin of the extremities the patient was well until 1934, when he began to have pain in his back. There was no history of trauma. He continued to work until December, 1935, when his back pain became too severe for him to continue, and he entered the hospital on January 16, 1936. The pain was mostly lumbar. It was continuous, did not radiate and was worse at night and on motion.

On the first physical examination the back appeared normal. The left leg was shorter than the right and the pelvis was tilted. The left knee jerk was increased. The left testicle was atrophic. Other findings were normal except for ichthyosis of the skin of the arms and back.

Routine examinations of the blood, urine and stools at this time were negative, as were a gastric analysis and Wassermann and Kahn tests on the blood and spinal fluid.

A lateral roentgenogram of the lumbar vertebra showed no evidence of fracture, dislocation, demineralization, or other bone abnormality. Fluoroscopic examination

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† I am indebted to Dr. Sloan for permission to report this case and to Dr. William Culpepper for the roentgenograms.

of the thorax and its viscera disclosed no abnormality. The esophagus, stomach and duodenum were negative for filling defects when examined after a barium meal, and, except for marked ptosis of the transverse colon, the lower intestinal tract was not remarkable.

On January 28, 1936, a moderate bowing of the spine to the right in the dorsal region and a lordosis in the lumbar region were noted. The left leg was shortened and both femurs were slightly bowed.

The diagnosis at this time was possible beginning Paget's disease.

The patient resumed work on February 1, 1936, but he was unable to continue and he returned to the hospital on May 5, 1936, where he remained until his death on October 30, 1936. He continued to have severe pain in the lower dorsal and lumbar regions. It was not relieved by removal of all of his teeth, traction, or by drugs which later included narcotics. His dorsal and lumbar spine now became fixed, and there was a kyphos in the region of the 8th dorsal vertebra.

On July 28th a neurological examination was negative. Spinal puncture yielded clear fluid with a cell count of 12. A guinea-pig injected with this fluid did not develop tuberculosis. On July 29th new roentgenographic studies showed ". . . a destructive process involving the bodies of the 4th, 5th, 6th and 9th thoracic vertebrae and the 1st lumbar vertebral body; also the transverse processes; the 12th rib on the left side and the 11th right rib, suggestive of malignancy. Mottled appearance of the pelvis suggestive of atrophic changes is present."

During August two small nodules appeared on the ribs, and in September non-traumatic fractures of the 6th, 7th and 8th ribs were noted. Numbness to the level of the knees developed in September. The urine showed albumin occasionally but was negative for Bence-Jones protein in August and in October. The patient had a severe progressive anemia. The pulse was constantly rapid. During May and June there was a daily afternoon fever with peaks at 99° to 100° F. Early in July a bout of fever with temperatures up to 102° F. was followed by temperatures at the former level. His appetite was poor and he had frequent emeses. Pain was intense. He became dyspneic in October, grew weaker and expired on October 30 1936. There was no x-ray or radium therapy.

The final clinical impression was that of a malignant tumor metastatic to bone, with the primary site undetermined.

Abstract of Necropsy Examination

The final anatomical diagnoses were: Multiple, diffuse fibrosarcomas of bones; extensive fibrosarcomatous invasion and destruction of the spine with kyphoscoliosis; fibrosarcomatous invasion and destruction of the sternum, ribs, clavicles, pelvis, upper ends of the humeri and femurs, sphenoid and parietal bones; fibrosarcomatous metastases to the lungs, liver, spleen, heart, pancreas, kidneys and adrenals; marked emaciation and anemia; brown atrophy of the heart and liver; generalized serous atrophy of fat; multiple cutaneous nevi; ichthyosis; atrophy of the right kidney and compensatory hypertrophy of the left; slight adenomatous hyperplasia of the adrenals; atrophy of the left testis; traction diverticulum of the esophagus; accessory spleen.

External Appearance. The body was that of an extremely emaciated, deformed and pale white male appearing about 55 years of age rather than the stated 43 years. The estimated weight was 100 lbs. and the

estimated length, 70 inches. The skin showed a marked ichthyosis, being thick, dry, branny and scaling. It was finely cracked and large shreds of dry epidermis could be pulled off almost anywhere. The skin also showed many flat, soft, pale brownish nevi up to 1 cm. in diameter. They were numerous on the trunk, both anteriorly and posteriorly, several dozen being visible. None appeared malignant on gross examination.

The body was deformed. The skull was large. The zygomatic arches were prominent, and the clavicles were very conspicuous. The sternum was deformed, having a deep transverse depression at the level of the junction of manubrium and body and another groove across the lower end of the body. The entire sternum, therefore, lay near the spine, and the chest was flat and long. The costal cartilages were concave and the costochondral junctions were knob-like. Several ribs had small fusiform swellings.

The extremities were wasted. The left leg was about 2 inches shorter than the right. The spine had several abnormal curvatures which will be described with the skeleton.

Body Cavities. Except that the upper two-thirds of the right lung was everywhere adherent to the parietal pleura by fibrous adhesions, the great body cavities appeared normal. The adipose tissue was scanty and dark.

Esophagus. At the level of the tracheal bifurcation there was a diverticulum of the esophagus which admitted half of the distal phalanx of the index finger. Externally it was firmly adherent to a scarred tracheobronchial lymph node.

Parathyroids. The parathyroids appeared about normal in size. They measured: Right upper, 4 by 3 by 1.5 mm.; right lower, 5 by 4 by 2 mm.; left lower, 4 by 4 by 1.5 mm.; left upper, 7 by 4 by 2 mm.

Heart. The heart weighed 300 gm. The epicardial fat was gelatinous and dark, the myocardium was brown and the endocardium was unusually opaque.

Lungs. Each lung had a number of flat, button-like, grayish white, neoplastic pleural nodules up to 1.5 cm. in diameter and not over 2 mm. thick. They had red margins. Scattered throughout the substance of all lobes were numerous hard, grayish white nodules up to 1 cm. in diameter. Similar tumors enclosed and thickened the walls of many bronchi.

Liver. The liver weighed 1510 gm. Through the thin capsule 15 to 18 firm whitish neoplastic nodules up to 2.5 cm. in diameter were visible. The larger tumors had umbilicated centers. Similar tumors were seen throughout the liver substance.

Spleen. The spleen weighed 190 gm. Under the capsule on the diaphragmatic surface there was a nodule, 8 mm. in diameter, and several smaller tumors were visible on the surfaces made by cutting.

Pancreas. One nodule, 4 mm. in diameter, was seen on the anterior surface of the pancreas.

Adrenals. The adrenals were enlarged, together weighing 17.5 gm. One had a yellow nodular area, 2 mm. in size, in the cortex. The other was diffusely enlarged by an infiltration of grayish white tumor, growing in both the cortex and medulla.

Kidneys. The left kidney was markedly atrophic, weighing 31 gm. Its artery was small but not occluded. The right kidney weighed 140 gm. Two firm, whitish nodules of neoplasm, measuring 1.2 and 0.3 cm., were seen in it.

Generative Organs. The left testis was small and fibrotic, while the right appeared normal. The seminal vesicles and the prostate were not remarkable.

Muscular System. The muscles were atrophic and pale. The fat and connective tissue around the muscles was gelatinous, resembling that of serous atrophy.

Skeleton. The calvarium was hard and thinner than usual. An osteolytic tumor, 1.5 cm. in diameter, had eroded both tables in the left parietal bone. The sphenoid was soft and largely replaced by firm, yellowish gray, neoplastic tissue, although its configuration was retained.

The spine showed a number of abnormal curves. In the lower cervical region it turned backward and to the left, forming a kyphoscoliosis, with a sharp angle in the upper dorsal region. It then overcompensated by passing to the right in the lower dorsal region. In the lumbar spine was another kyphoscoliosis to the left. The pelvis was tilted, and it was higher on the left. There were no visible or palpable abnormalities in the bones of the pelvis.

With the knife a wedge-shaped segment was cut from the vertebral column, which appeared comparatively normal externally except for the abnormal curves already described. This wedge of bone was removed with ease from the cervical region to the sacrum. Examination then disclosed that the vertebral bodies were almost entirely replaced by firm, yellowish white tumor. Consequently they were very soft (Fig. 4). Some of the vertebral bodies had collapsed so that they were narrower than the intervertebral disks.

The sternum was angulated and deformed, as previously described. Pieces could be cut from it with ease with the knife at any point (Fig.

4). Both cortex and marrow spaces appeared to be replaced by tumor, although the bone was not enlarged.

The ribs lay near each other because of the partial collapse of the spine and the sinking of the sternum. They could be bent and fractured with ease, and they could be cut with the knife (Fig. 4). The 5th, 6th and 7th left ribs showed slight fusiform enlargements at the sites of previous fractures.

When the lower end of the upper third of the left femur was opened it was found to be of normal hardness. The cortex was thick and the marrow cavity was small. One small neoplastic nodule was seen eroding the cortex from within at this level (Fig. 4).

No bony enlargement resembling a primary tumor site was seen anywhere in the skeleton.

Post-mortem Roentgenograms. Because all bones could not be examined thoroughly at necropsy, post-mortem roentgenograms were made of the trunk, legs and humeri. The femurs showed outward bowing and irregular osteolytic lesions in the center of the upper third, head and neck. Each femur showed a few sharp, osteolytic lesions, about 3 mm. in diameter, in the upper part, but the bones of the leg below this level showed no abnormality. The remainder of the skeleton, except for the distal two-thirds of each clavicle, showed marked demineralization and deformities as described. The cortex of the bones was greatly thinned or entirely absent. Numerous, irregular, confluent osteolytic lesions in each bone were responsible for the osteoporosis.

Histopathology

Only those histopathologic changes which are considered pertinent will be described.

The Tumor. The tumor was composed of spindle cells which, in the sections of bone, were long and slender, but which, in the visceral metastases, were more pleomorphic, although the spindle form was dominant. The nuclei in general were spindle-shaped, but some were irregular. They were usually of medium size but a few giant forms were seen. The chromatin was slightly clumped and scanty, and some hyperchromatic nuclei were found. Mitotic figures were few. The cytoplasm was poorly seen because it was slight in amount and because of the large amount of intercellular fibrillar and mucinous material. The fibrils stained like collagen by the van Gieson, Mallory, and Masson methods. With the Mallory phosphotungstic acid-hematoxylin stain the fibrils were seen to be predominantly adjacent to and not in the cell cytoplasm. Silver impregnation by Perldau's method revealed

much reticulum in the more cellular parts of the tumor. Collagen was abundant in all sections but the greatest amounts were found in the sections of bone. The stroma in many places had a bluish, mucoid appearance, but such regions stained poorly or not at all with mucicarmine.

The cells grew, in general, in the form of broad bundles, but in a few places they had an irregular, whorl-like growth, and elsewhere the growth was even and diffuse. The tumor contained few blood vessels. There was no necrosis. Nowhere did it form bone or cartilage, and no definite osteoid tissue was seen. A fine brown pigment was seen in the tumor in the liver, spleen and bone marrow. This gave a positive Prussian blue reaction for iron and it failed to react positively with Masson's silver impregnation method for melanin. Since a similar pigment was found in these locations apart from the tumor, it was not considered significant.

Bones. The neoplastic growth in many sections of the bones completely replaced the marrow, from which it appeared to have arisen. It destroyed trabeculae and cortex, eroding through the latter in many places. In such places it elevated the periosteum but little or not at all, and it stimulated no periosteal new bone. While occasional tumor cells infiltrated the surrounding soft parts in a few places, no extracortical tumors were formed and the configuration and size of the bones was remarkably well preserved. The tumor was osteolytic, apparently by direct action as well as by stimulation of osteoclasts. Small pieces of necrotic bone enclosed by tumor were found. At one point was seen some calcification in dense collagen.

Vertebral Body. Both cortical and cancellous bone was almost completely destroyed by the tumor, which was here very fibrous. The tumor cells infiltrated the intervertebral disks. Small calcospherites (possibly artifacts) were numerous.

Rib. At this point the rib was almost entirely replaced by tumor, although islands of cortex persisted. There was no sign of repair in an old fracture.

Sternum. Here also was seen total replacement of the bone marrow and nearly complete destruction of the bone itself. Although, as elsewhere, tumor cells penetrated the periosteum, they failed to form extra-osseous tumor masses.

Femur. At the lower end of the upper third of the femur there was a solitary, osteolytic neoplastic nodule, 1 cm. in diameter, eroding the cortex from within. From this point tumor cells were infiltrating the marrow spaces and into the haversian canals. Osteoclasts were

exceptionally numerous here. Elsewhere this bone and its marrow were normal, the latter showing active hemopoiesis.

Visceral Metastases. In the viscera the metastases were fairly sharply circumscribed but infiltrative. The tumor cells tended to invade the surrounding tissues and to incorporate some of the more resistant structures within their limits.

Adrenals. A noncircumscribed metastasis was present in an adrenal. This centered in the medulla and reticular zone, and grew out between the cells of the fascicular zone in delicate linear rows. Another section showed a nodular area composed of atypically arranged cortical cells.

Heart. The endocardial opacity seen grossly was found to be due to an infiltration of the subendocardial region by metastatic tumor, which also extended into the myocardium, particularly along the perivascular connective tissue. A papillary muscle was sheathed by a similar growth.

Lungs. The tumor formed flat masses in the pleura, sheathed some of the blood vessels and bronchi, and infiltrated into the surrounding lung. In some places an exceptionally large amount of mucoid stroma was found.

Liver. In the liver the tumor formed distinct nodules in which the cells showed the greatest degree of pleomorphism and the most whorling.

Spleen. The metastases were poorly circumscribed and highly infiltrative in the spleen.

Kidney. The tumor infiltrated the kidney parenchyma and included the remains of kidney structures. Numerous small metastases, not seen grossly, were present. The stroma was very mucinous, even in the smallest metastases.

Pancreas. One small metastasis was seen in the pancreas.

Miscellaneous. Brief reference is made to additional structures in which no metastases were found.

Parathyroids. No abnormality was seen in the parathyroids except that the oxyphil cells were possibly more numerous than usual at this age.

Skin. There was marked hyperkeratosis and some follicular plugging of the skin. Aside from this the epidermis was very thin, in some places being only six cells thick. The papillae were slender, long, sometimes clubbed and occasionally connected. There was an irregular increase in melanin. The dermis contained a collection of nonpigmented nevus cells. There was no fibrosis or inflammation of the dermis.

DISCUSSION

In summary, this was a purely osteolytic, slightly anaplastic fibrosarcoma which was widely disseminated throughout the hemopoietic and reticulo-endothelial areas of the skeleton, where it replaced the bones without causing enlargement suggestive of a primary site. There were small metastases in many viscera. In addition there was ichthyosis.

Two views about the nature of this tumor present themselves. One is that it represents widespread sarcomatous change in Paget's disease. The other is that it is a peculiar fibrosarcoma probably arising from the medulla of bone and possibly multicentric in origin, and thus related to the myelomas, which it resembles in its distribution and behavior. While it is impossible, from the available evidence, to decide between these two theories, it is my opinion that the latter explanation is more probable. Evidence for both views, and others, will be presented, together with the opinions expressed by some of the consultants.

The main reasons for considering the diagnosis of Paget's disease with sarcomatous change are the pelvic deformity and the bowing of the femurs. The roentgenograms show a change which might be interpreted as new bone formation above the acetabulum, in the trochanters and on the concave side of the femurs.

Against the diagnosis of osteitis deformans is the failure of any section of bone to show the changes characteristic of this disease. There is no new bone formation and the fibrotic tissue can all be regarded as fibrosarcoma. The skull was thin and hard. The tibia showed no roentgenographic changes, and nowhere else are the films typical for this disease. The bones were not thickened or deformed. Furthermore, extensive Paget's disease is unlikely at this age.

Additional reasons for considering this to be a bone sarcoma which arose independently of Paget's disease are its rapid course of 10 months, counting from the time a physician was first consulted. In January roentgenograms were negative and in July destructive lesions were well advanced. At no time were the roentgenographic changes characteristic of Paget's disease.

The question as to whether this tumor was solitary or multicentric in origin cannot be settled at the present time any more than it can with plasma cell or other myelomas. The fact that on the first roentgenographic examination of the skeleton no lesions were found, while 6 months later they were widespread, indicates either simultaneous origin in many places or rapid metastasis. The apparent origin, almost simultaneously, in many bones and the absence of one lesion larger than the others suggest multicentric origin. Multiple, independent

primary tumors in bone, other than myelomas, have been described but they are not common. The distribution in the skeleton, namely, that of the hemopoietic and reticulo-endothelial marrow, cannot be used as evidence either way, because it is common to myelomas and to extensive neoplastic metastasis to bones from within or from without the skeleton.

The presence of marked skin changes, here called ichthyosis, which preceded the development of the bone sarcoma is of interest. No causal relationship has been established between these two conditions, but neither has this possibility been excluded. The thick, dry, scaling skin was stated to have been present for many years, and it became worse as the cancer cachexia developed.

In view of the marked skin changes, as well as some profound alterations in the connective tissues, leading in the connective tissue of bone to sarcoma, a nutritional disturbance, possibly in the nature of vitamin deficiencies, was suspected. No positive evidence for such factors could be found. No history of past dietary deficiencies, indiscretions, or food likes and dislikes could be elicited.

The question also arises as to the relationship, if any, of the nevi in the skin to the osseous sarcoma. Could this be an example of widespread melanosarcoma metastatic into bone, or could it be an extensive disorder of the neuro-ectoderm with nevi in the skin and neurogenic sarcoma in bone? There are good reasons for rejecting the first of these hypotheses: None of the nevi appeared malignant, the cytological appearance of the tumor was not that of melanosarcoma, and there was no melanin in the cells, even by special staining methods. The second idea is less easily disposed of, but neither is there any strong evidence in its favor. While neurogenic sarcomas commonly consist of a spindle-celled growth with whorling, scattered giant cells and a tendency to mucinous degeneration in the stroma, they do not have any known special affinity for the skeleton, either as primary tumors or as metastases. A generalized neurosarcomatosis of the skeleton has not been described to my knowledge, but localized cases have been described. Also, in most areas, the tumor did not resemble the structure of neurogenic sarcoma but was more like that of the ordinary fibrosarcoma. The skeletal changes sometimes seen in cases of von Recklinghausen's neurofibromatosis are unlike those in the present case.

Several consultants, in their reports which are quoted below, emphasized a point which has not hitherto been stressed, namely, that some of the lesions, even in viscera, appeared more like independent foci giving rise to sarcoma than like metastases. This idea is based

on the diffuse, highly infiltrative nature of such areas. There is, however, no gradual gradation from nonneoplastic to sarcomatous connective tissue cells at the margins of such areas but only admixture of these two types of cells. In my opinion the situation is analogous to that found in some carcinomas of the pancreas in which areas are found which appear to consist of precancerous epithelial cells, although probably such is not the case. Grossly, in the present example, the visceral tumors appeared like ordinary metastases. They were distinctly circumscribed.

Excerpts from the written opinions of several consultants are as follows:

Dr. Fred W. Stewart wrote: "I . . . do not recognize any known disease. Some of the visceral lesions are consistent with metastases but some are not. The fine interstitial fibroses in lung, heart, kidney and adrenal seem part of a general morbid change in connective tissues. The clinical association with extreme ichthyosis is at least remarkable if we merely throw it into the category of Paget's, especially since the bone lesions are not classical of Paget's, nor is extensive Paget's apt to occur at 43."

Dr. E. A. Codman expressed the opinion that: "My best guess is that this is an instance of Paget's disease in which the osteolytic phase far exceeds the osteogenic. . . . The marrow spaces in Paget's disease always show fibrosis. In this instance the fibrosis, by its superlative character, becomes a generalized new growth, just as in many cases of Paget's disease in which a localized sarcoma forms. In this case the process seems to be diffuse. . . . The metastases resemble those in cases of osteogenic sarcoma arising in Paget's disease, *i.e.*, they are nondescript and not very characteristic of having arisen in the bone. I see no evidence to indicate whether the metastases in this case arose from a single tumor or from different foci, but I believe there is evidence of diffuse malignant changes in several bones."

Dr. James Ewing wrote in part: "This case is quite peculiar and I do not remember anything like it. There are some features resembling spindle cell medullary sarcoma of the sclerosing type such as one sees in the medulla of long bones. These features are origin in the medulla, spindle cell structure, osteolytic tendency, absence of bone production and cellular areas suggesting a capacity to give metastases. The multiple tumors may be explained as metastases, but this origin is far from clear. The distribution especially about the spine and in the sternum is very peculiar and suggests rather a primary multiple origin, which is unknown with sclerosing spindle cell bone sarcoma. I do not see enough of the features of Paget's disease to warrant one in including

the case among the sarcomas arising in this disease, where, however, it may possibly belong. The most peculiar and significant feature is the apparent beginning of the proliferative process in organs outside of bone, as adrenal, heart muscle and lung. Here the process is not that of a metastatic lesion, but one finds the very earliest stages of proliferation of spindle cells about fine blood vessels, especially in heart muscle and adrenal. These lesions suggest an universal tendency to proliferation of perithelial cells similar to that seen in some forms of vitamin deficiency. What is the meaning of the extensive ichthyosis of the skin? This has certainly nothing to do with Paget's disease and indicates the presence of some general nutritional dyscrasia."

Dr. Kurt Apitz of the University of Berlin expressed the following opinion and stated that it was that also of Professor Hamperl: "This is—as you rightly put it in your diagnosis—a generalized sarcomatosis of the bones and viscera. The histologic appearance of the tumor is roughly that of a fibrosarcoma, but in its finer details it is quite unusual. I have not seen before such a regular whirl-like arrangement of collagen fibres, except in neurogenic tumors; but the latter origin has little probability for other reasons. I rather think the tumor might be derived from periosteal tissue. If the primary is small, it is quite possible that you cannot differentiate it from the widespread metastatic growth. The sections of the bones are very interesting because they show a peculiar type of calcification, a slight tendency towards osteoid formation, and intensive osteoclastic bone destruction. I do not see how the diagnosis of Paget's disease could be justified. There is only overwhelming metastasis in the marrow, and no other newly formed fibrous tissue, and there is no new bone with mosaic structures."

SUMMARY

An osteolytic fibrosarcoma of bone is described in which the lesions appeared at approximately the same time in many bones, and in which the tumors, although highly infiltrative, retained the normal configuration of the bones. The distribution and extent of the sarcoma was that of the hemopoietic and reticulo-endothelial areas in the skeleton. There were small metastases in many viscera. It is believed that this is an example of a medullary fibrosarcoma somewhat analogous to the myelomas, and that it, like them, might have had a multicentric origin.

[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 157

- FIG. 1. Post-mortem roentgenogram showing osteolytic lesions in the humeri, ribs, spine and scapulae. Segments of two upper left ribs were removed and are shown in detail in the lower center of Figure 4.
- FIG. 2. Post-mortem roentgenogram showing destructive lesions in the sacrum, pelvis and femora together with slight bowing of the latter. The bone fragment removed from the left femur is shown in Figure 6.

1



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Steiner

Multiple Diffuse Fibrosarcoma of Bone

PLATE 158

FIG. 3. Post-mortem roentgenogram of the lower spine and pelvis, showing osteolytic lesions.

FIG. 4. Roentgenogram of a segment of spine showing marked focal and diffuse bone destruction with collapse of several vertebral bodies, and retention of the normal osseous configuration; also (lower left) a segment from the center of the sternum, two left upper ribs (lower center), and a segment of the left femur (lower right), which, by contrast, is underexposed.

FIG. 5. Portion of liver showing numerous metastases. These were the largest of the visceral metastases.

FIG. 6. Segment of cortex of the left femur showing one osteolytic lesion.

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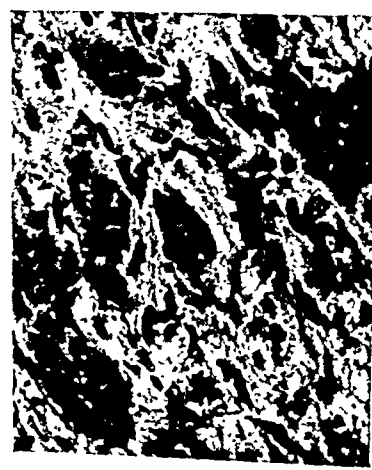
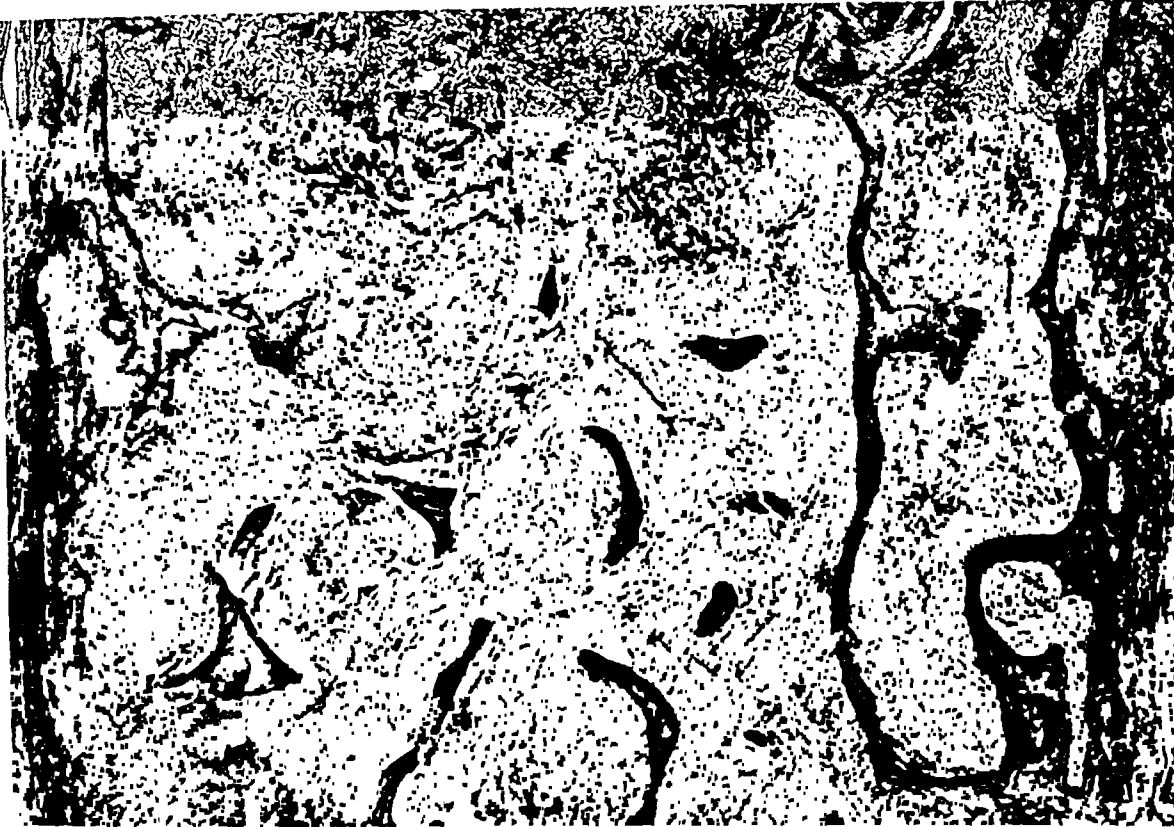


Steiner

Multiple Diffuse Fibrosarcoma of Bone

PLATE 159

- FIG. 7. Photomicrograph through the center of the sternum showing replacement of the marrow by tumor, partial destruction of trabeculae of bone and invasion, with focal penetration of the cortex and periosteum. $\times 20$.
- FIG. 8. Tumor metastasis to the heart. A papillary muscle is enclosed by tumor which also replaces the endocardium and invades the myocardium. $\times 42$.
- FIG. 9. High power photomicrograph showing the details of the tumor cells in the sternal bone marrow. $\times 395$.
- FIG. 10. Lower power photomicrograph showing the most anaplastic and pleomorphic growth which the tumor exhibited. This was in the liver. $\times 225$.
- FIG. 11. The manner of tumor infiltration through the adrenal. Similar growth was seen in the pancreas, kidneys and spleen. $\times 225$



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Steiner

Multiple Diffuse Fibrosarcoma of Bone

PRIMARY CARCINOMA OF THE LIVER WITH METASTASES TO BONE

REPORT OF A CASE *

META A. NEUMANN

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Primary carcinoma of the liver is a relatively rare neoplasm. A comprehensive survey by Charache¹ gives the incidence of such growths as 0.506 per cent in 509,772 autopsies. These figures were compiled from institutional records in various countries. Other studies²⁻⁴ give a somewhat lower percentage. The ratio is apparently higher among the negroes of South Africa and in Orientals.⁵

In a series of 8,200 autopsies at St. Elizabeths Hospital, primary hepatoma (composed of parenchymal liver cells) has occurred eight times. There were no carcinomas originating in the hepatic bile ducts (cholangiomas). Two cases occurred early in the autopsy series. From these no slides are available for a confirmation of the diagnosis and a histologic description is lacking. Metastatic growths in the lungs were reported in one of them. The six fully verified cases were of the multiple nodular type. The smallest number of tumor nodules was two. In three instances the neoplastic cells showed a more or less uniform structure and little anaplasia. There was an associated cirrhosis in four instances. No other demonstrable primary focus was present.

The following presentation describes the only verified instance of primary carcinoma of the liver with metastases at this hospital. The secondary growths were found only in the osseous system. Charache¹ stated that 20 per cent of all primary carcinomas of the liver metastasize to the lungs; 1.6 per cent to the skeleton. His figures appear representative. In 1937, Bolker, Jacobi and Koven⁶ found only nine cases with bone metastases reported in the literature. Three additional occurrences have been reported since their survey.⁷⁻⁹ A number of the reported cases of primary carcinoma of liver show no extrahepatic metastases.¹⁰⁻¹² The condition occurs much more commonly in males than in females.

REPORT OF CASE

History. A colored female, 55 years of age, was admitted to St. Elizabeths Hospital in 1936. As far as is known there were no significant findings in her early history. The patient never went to school, and never learned to read and write. She worked as a domestic and laundress until the day she was hospitalized. The patient had been alcoholic, but in the previous 5 years had refrained from drinking as it interfered with her work.

For some time she had complained of "swimming" in the head, but continued to follow her regular routine until September 13, 1936. On that day she was sent by the police to the House of Detention on the assumption that she was drunk.

* Received for publication, November 30, 1943.

She denied having taken any liquor, but said that she had a headache and a "swimming in her head." The next day she was transferred to Gallinger Hospital, and 2 weeks later she was admitted to this hospital.

She was emaciated, tremulous, and showed beginning arteriosclerotic changes. There was marked asymmetry of the face. Pupils were equal and round, and did not react to light or in convergence. Her tongue protruded tremulously to the right on extension. There was a definite motor speech defect. Marked tremors of face and fingers were noted. The gait was unsteady. There was slight swaying to the right in the Romberg position. Deep reflexes were sluggish. Patellar reflexes were equal but diminished. There was no ankle clonus, and no Babinski sign. There was no evidence of glandular dyscrasia.

The clinical and mental diagnosis, confirmed by serologic and colloidal gold tests, was general paresis.

In the following 5-year period she showed no significant physical changes. She received extensive antiluetic treatment, including several inoculations with tertian and quartan malaria. She was also given an intravenous typhoid vaccine in January, 1937, which was followed by paralysis of the left half of the face, diagnosed as a peripheral paralysis of the seventh nerve. In September, 1937, weakness of the right side was noted by the physician.

In September, 1941, a cyst was observed in the upper portion of her forehead near the midline. The medical protocol stated: "It was crepitant around the margins and was accompanied by two smaller cysts in the neighborhood. X-ray of the skull showed several circular areas of lessened bone density, surrounded by areas of increased bone density." They varied in size from a dime to that of a half-dollar. Blood was withdrawn from these areas on puncture, so no attempt was made to remove tissue for biopsy.

Bones of the pelvis and legs showed no lesions. A tentative diagnosis of multiple meningeal hemangioma was made. Roentgenograms and fluoroscopy of the chest, abdomen and gallbladder were negative.

On December 18, 1941, the patient complained of pain in the left arm. Radiographic examination showed that the entire left humerus was involved in a malignant process. The roentgenologist considered this a metastatic lesion from the skull and modified the original diagnosis to hemangiosarcoma. On December 23, 1941, arteriography of the cranium and contents showed that the large frontoparietal tumor was in the skull and extraneous to the inner table. There was no marked alteration in the normal pattern of the intracranial vessels. Repeated electroencephalograms showed abnormal wave-forms in the right frontal region.

Radiography of the spleen was performed 4 days later. The roentgenologist reported shadows in the regions of both liver and spleen. He stated that "the shadows are not homogeneous, but spotty. They contain areas of radiolucency, which raise a suspicion of absence of organ tissue, with replacement by malignant tissue in these particular spots." On January 20, 1942, a radiograph of the femur showed a small area, about the size of a dime, in the lower third. This was considered as representing another metastatic lesion. During this period the masses in the skull were gradually enlarging. The site of the primary growth was not determined.

The patient grew progressively weaker and died on January 28, 1942.

Necropsy Findings

Autopsy was performed 6 days after death. The body was emaciated. A firm mass was palpated in the midportion of the humerus. There was abnormal movement and crepitation in this region. A large,

rather soft, fluctuant mass, about the size of an orange, was present in the right frontal region. The hair over the tumor was normal. No other abnormalities were noted on external examination.

The scalp was easily dissected from the tumor, and was nowhere invaded. The large frontal tumor was hemispherical in shape, its base measuring about 8 cm. in diameter. It had a smooth, dark red surface, traversed by blood vessels (Fig. 1). Several small hemorrhages were observed. The growth was distinctly fluctuant. It had completely eroded the skull cap, but apparently did not invade the dura. There were four other smaller metastatic lesions in the skull cap; none grossly penetrated the dura. The dura was markedly adherent to the skull cap, and no attempt was made to separate it.

Metastatic lesions were not present in the leptomeninges or brain. There was an old area of infarction in the right third frontal convolution. Cross sections showed that this lesion involved part of the adjacent insula, capsula externa and claustrum.

Examination of the thoracic cage showed no evidence of tumor growth. The heart was small and flabby. Coronary arteries and aorta showed arteriosclerotic changes, and there was evidence of luetic aortitis. The lungs showed congestion, edema, and beginning bronchopneumonia in the left lower lobe.

The liver was markedly enlarged and filled the entire upper half of the abdominal cavity. The surface was nodular and studded with large and small tumor nodules, which varied in size from 0.3 to 10 cm. On palpation the large, dark hemorrhagic nodules were fluctuant, while smaller white tumors were firmer. The largest nodule at the lateral border of the right lobe, just beneath the diaphragm, superficially resembled the cranial growth.

A flat section through the liver gave rise to the impression that there were three types of tumor growth (Fig. 2). The most numerous type produced nodules which were round, and of the yellow color of adrenal cortex. They were extremely soft, even partially liquefied, and showed no structural detail. They seldom averaged more than 1 or 2 cm. in diameter. These growths were usually well circumscribed. The second type consisted of white, firm nodules sharply demarcated from the hepatic parenchyma. The large encapsulated tumor in the right lobe was representative of the third type. It was fairly firm, and its cut surface lacked the homogeneous appearance of the other types. At the periphery there were mottled, hyperemic, yellowish red areas showing numerous hemorrhages. Translucent grayish white bands formed irregular septa between such areas. The central part of the growth was soft and yellowish. It was estimated that more than half of the

liver was replaced by neoplastic tissue. The intact parenchyma was turbid, dark reddish brown, and its architecture was indistinct.

Other parts of the gastrointestinal system were free from disease.

In the genitourinary system there were no significant findings. The kidneys were congested and showed arteriosclerotic changes. There were several characteristic fibromyomata in the uterus. They showed no resemblance to the tumors in liver or cranium.

The lymph nodes showed no trace of metastatic growths. They were nowhere enlarged. The spleen, likewise, showed no abnormal changes.

The right lobe of the thyroid was enlarged to about the size of a small lemon, while the left lobe had normal dimensions. The surface was nodular. No normal thyroid tissue was found on sections. There were many small cysts, which were either empty, filled with grayish, gelatinous material, or with blood-tinged fluid. The solid portions of the gland were grayish and translucent.

The suprarenal glands were of average size and shape. The cortex and medulla were well preserved. In the right adrenal there was a yellowish nodule, 3 mm. in diameter, which was not sharply demarcated from the cortex.

Two metastatic tumors were found in the vertebral column. One had invaded the caudal part of the body of the 7th cervical vertebra. The other growth, in the lower thoracic and upper lumbar regions, had invaded the vertebral disks and adjacent ribs. Both of these tumors were composed of very soft, yellowish tissue, resembling certain of the nodules in the liver. They showed no structural detail.

A 6 inch length of humerus was removed from the middle of the shaft, including the site of neoplastic fracture. The fracture line was roughly parallel to the long axis of the humerus. It was about 4 cm. in length. In the region of the fracture no normal bone cortex was observed. The ill-defined medullary region showed circumscribed, soft, yellow areas and several hemorrhages. There was marked decrease in consistency of the bone, and no sharp distinction between cortex and medulla.

After fixation for several days in formaldehyde solution, the liver and the cranial and other osseous tumors were re-examined. Some of the tumors, which in the fresh state were yellow, had changed to a soft green, resembling patina. This was especially pronounced where the tissue had been in direct contact with formaldehyde. A section through the middle of the humerus did not show this color change. Strangely enough, the green color disappeared after the specimens had been in formaldehyde for about 1 week.

Sections through the large cranial tumor showed dark reddish brown

areas with several small hemorrhages. There were rounded, yellowish areas beneath the thick outer capsule, and adjacent to the dura. The tumor showed central necrosis.

Although the liver seemed the most likely source of the primary growth, the bright yellow color of many of the nodules led to the suspicion that the tumor might have originated in aberrant adrenal tissue. No definite diagnosis could be made from a supravital preparation of a soft, yellowish hepatic tumor, as the faintly granular or vacuolated cells resembled those of either liver or adrenal cortex.

Microscopic Examination

Detailed histologic studies from widely separated areas in the liver clearly established that the primary neoplastic focus was in that organ. The microscopic picture varied considerably in different tumor nodules.

The large encapsulated growth in the right lobe showed marked anaplasia. The normal lobular arrangement was completely lost, but in many areas the tumor cells formed cords separated by narrow clefts. Individual cells, too, were often separated by narrow unstained spaces. The cells comprising the cords were hypertrophied and had deeply stained acidophilic cytoplasm. The darkly stained nuclei frequently assumed bizarre shapes. Lobulated nuclei and signet-ring forms were not uncommon. There were many multinucleated cells; those with two nuclei predominated. The cells showed wide variation in size. Some of them contained bile pigment. Fat vacuoles were numerous.

In general, the clefts between the pseudo-cords were lined with cells which had slender, dark nuclei. Some of the narrow spaces contained a few erythrocytes. The scanty cytoplasm of these cells was occasionally seen to terminate in thin processes.

This growth was highly vascularized. In certain areas the cell cords radiated from an engorged thin-walled vessel (Fig. 3) but never showed a true lobular arrangement. There were many hemorrhages. No tumor thrombi were demonstrable, but occasionally a few tumor cells clung to the lining of a vessel.

There were no bile ducts in the neoplastic tissue. A few isolated ducts were present in the thick connective tissue capsule at the periphery. Dense fibrous tissue separated irregular groups of lobules. A small hemangioma was present in one fibrous band.

Variation in size of cells was a striking feature in all the tumor nodules. In certain areas there was a tendency for the cells to form acini (Fig. 4). Some of the acini were lined by a single layer of cells; in others the lining cells were piled up in disorderly fashion to form several irregular layers. There was no uniformity of structure. Some

of the acini contained red blood cells or a few delicate pink-stained shreds. It should be noted that in those spaces containing erythrocytes there was no endothelial lining; the slender dark cells lining the clefts were on the *outside* of the acini. The irregular anastomosing cords merged gradually with the acini.

Histologically one could not differentiate the white, green and yellow tumor nodules of the gross specimen. Bile pigment was recognized in some areas, and, where hemorrhages occurred, hemosiderin pigmentation. One tumor nodule was composed of an almost solid sheet of epithelial cells. The cells were small and had a pale, foamy cytoplasm.

The hepatic parenchyma which was not involved by the neoplastic process had lost all traces of normal structure. It was the seat of a long-standing cirrhosis. There were isolated cords or small islands of liver cells which showed no true lobular arrangement. Fibrous tissue was moderately increased. There was widespread necrosis. The sinusoids and other venous channels were distended with erythrocytes in varying stages of degeneration. There was extensive hemosiderin pigmentation. Kupffer cells were unusually prominent because of their enclosed pigment. There were a few focal accumulations of lipoid globules. Bile duct proliferation was not marked.

The metastatic growths in the skull, vertebra and humerus showed similar variations in structure. There was no trace of normal bone marrow in the humerus. In the large central neoplasm more or less orderly cords of epithelial cells predominated. They were usually separated by clefts lined with thin, dark nuclei. Many of the spaces between the cells were distended with erythrocytes. The cells were fairly uniform in size in this region but in other secondary growths anaplasia was an outstanding feature. In one tumor from the vertebral column there were many enormous acidophilic cells with lobulated pyknotic nuclei (Fig. 7). These cells merged gradually with alveoli of various sizes, lined usually with smaller cells. The bizarre giant cells sometimes formed acini, but more frequently showed the more characteristic cord structure. In the adipose tissue surrounding the growth there were several medium-sized vessels filled with tumor thrombi (Fig. 8). It was noteworthy that even inside the vessels the tumor cells persisted in reproduction of typical cords separated by narrow spaces which usually contained red blood cells.

In the large tumor of the skull there was extensive necrosis. In the well stained areas many acini had formed (Fig. 6). In other areas the resemblance to hepatic tissue was startling (Fig. 5). The only stroma was the capillary system between the anastomosing cords. The dura showed infiltration with tumor cells in one area. Some of the

metastatic tumor cells contained greenish brown pigment granules. No bile duct formation was found in any of the secondary growths. Fragments of bone were sometimes found deep in the tumor.

The thyroid tumors were classified as fetal adenomas and contained many cysts. The cell picture in no way resembled that of the hepatic or skeletal tumors. The area in one adrenal which aroused suspicion turned out to be only nodular hyperplasia. Many of the organs showed marked congestion and stasis.

Sections from the brain showed very little evidence of an active syphilitic process. The infarct in the frontal lobe was old. There was no evidence of tumor metastases in the central nervous system.

COMMENT

Most observers agree that the diagnosis of primary liver carcinoma *intra vitam* is difficult and seldom made, and that the duration of symptoms is relatively short, usually only a few months. The symptoms due to lesions in the osseous system, often a spontaneous fracture, may be the first clinical evidence of a physical disturbance. Although the nature of the bony lesion is easily identified by roentgenogram, the location of the primary growth is usually identified only at autopsy.

The most striking feature of these neoplasms is the reproduction of tissue resembling hepatic parenchyma in distant metastases; ^{5, 6, 13-15} that is, anastomosing cords of epithelial cells separated by endothelium-lined spaces. These cells are apparently able to carry out at least one of the functions of liver cells, namely, the production of bile pigment, as indicated by the green color of the tumors grossly and the histologic identification of the pigment granules. This type of neoplasm is therefore called organoid, rather than histoid, since the metastases give "morphologic evidence of the original physiologic function." ⁶

The variegated color scheme of hepatomas has been noted by practically all observers. Mallory ¹² commented on the color change from yellow to green in material fixed in formaldehyde, similar to that observed in our case. He stated: "That is the usual reaction when bilirubin is oxidized by formalin. . . . This appearance could mean that the tumor cells were producing bile and that since they were not connected up with any bile ducts it remained in the tumor."

Ewing ¹⁵ also discussed the secretion of bile in secondary growths. He stated that: "Bile secretion diminishes with increasing anaplasia." In the reported case it was noted that the tumors which were least typical of liver structure were paler and firmer than the green nodules.

The association of cirrhosis with primary hepatoma is referred to by many authors, and excellently summarized by Ewing. ¹⁵ He stated

(p. 722) that "there is little doubt that cirrhosis, and the factors that lead to it, cause degeneration followed by regenerative overgrowth which may become excessive and neoplastic." Charache¹ also felt that the association is too frequent to be a mere coincidence.

There is less agreement on whether the primary focus in the liver is single or multiple. Certain authors^{3, 4, 6} believed that those cases which exhibit many tumor nodules throughout the liver show this feature by virtue of intrahepatic dissemination through the portal system. Other observers^{1, 15, 16} believed in the multicentric origin of the tumors.

No proof of either theory is furnished by this case. Although samples of tissue were taken from several areas of the liver, all of which were well vascularized, no tumor thrombi were found in any section. In the reported cases which showed only a single hepatic growth it was usually found in the right lobe. Certainly in the case reported here, the right-sided tumor was the largest. It is suggested, however, that the existence of multiple primary foci may be explained as a corollary of the theory that hepatic carcinomas are the sequelae of nodules of regenerating epithelium following cirrhosis. This theory, however, would not offer an explanation for the occurrence of multiple tumor nodules without cirrhosis.

SUMMARY

A case of primary carcinoma of the liver (hepatoma) with metastases to the skeleton is described. The distant metastases reproduced the architecture of the primary, with anastomosing cords of epithelial cells, separated by spaces lined by endothelium. In the areas of better differentiation there was evidence of the formation of bile.

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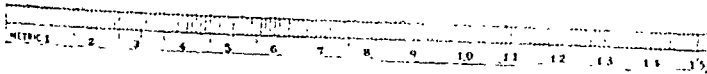
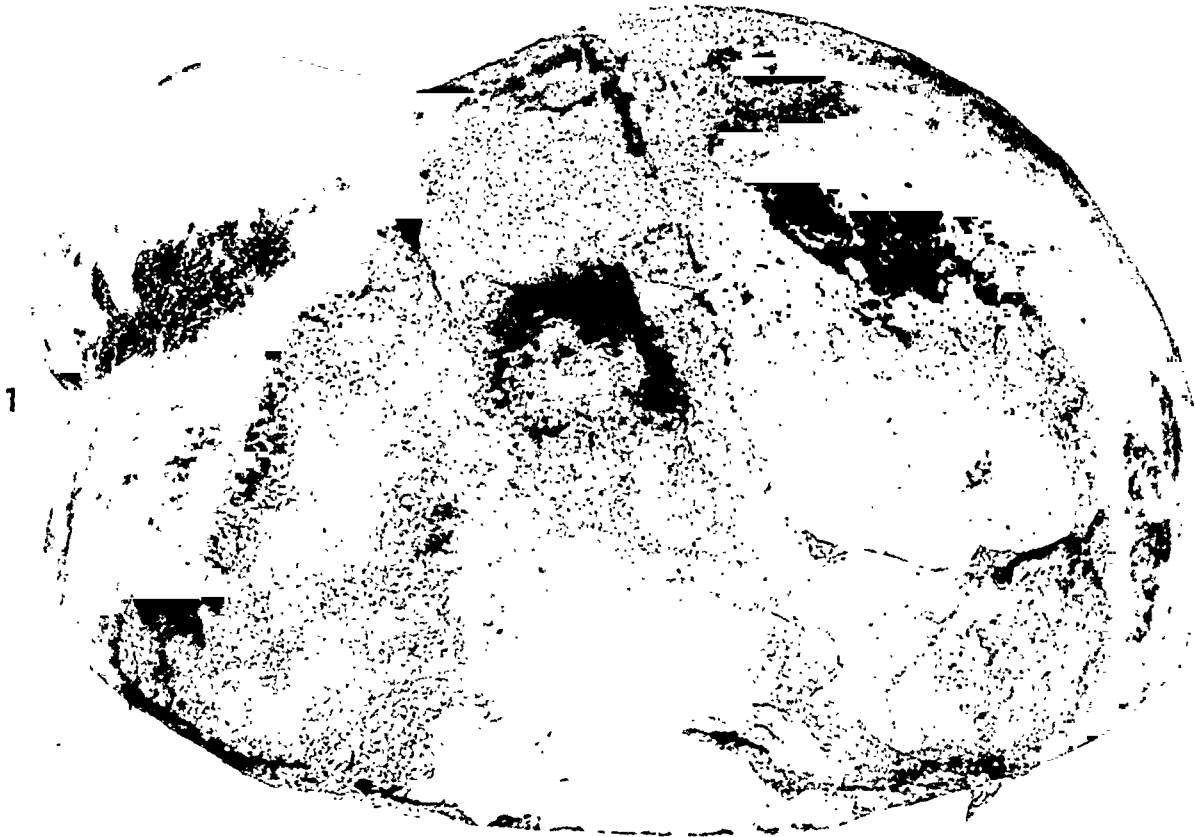
[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 160

FIG. 1. Gross photograph of the cranium, showing metastatic hepatomas.

FIG. 2. Gross photograph of the liver, showing primary carcinoma (hepatoma) and multiple nodular tumors.



Neumann

Primary Carcinoma of the Liver

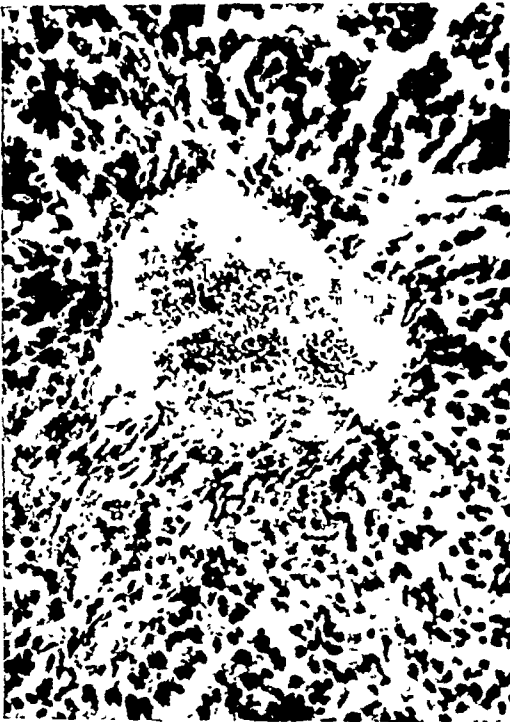
PLATE 161

FIG. 3. Liver. Primary carcinoma. Tumor cells radiating in short cords around thin-walled vessel. Multiplication of slender, dark nuclei around blood space.

FIG. 4. Tumor cells forming irregular acini.

FIG. 5. Metastatic hepatoma in cranium. Liver-like structure of neoplastic cells.

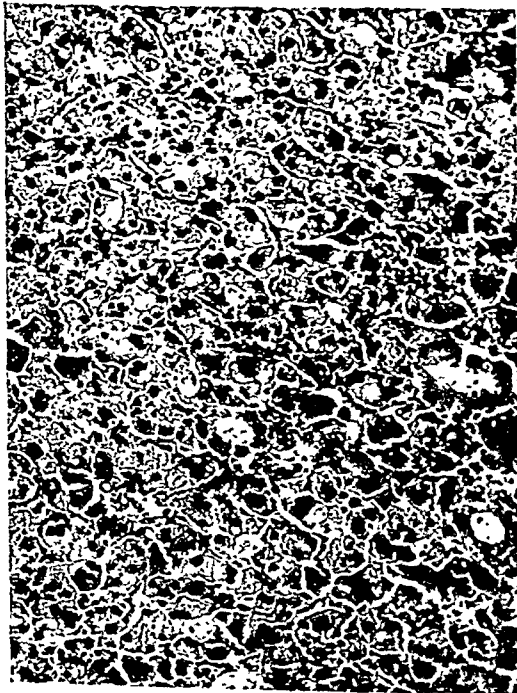
FIG. 6. Metastatic hepatoma in cranium. Tumor cells form branching columns and acini.



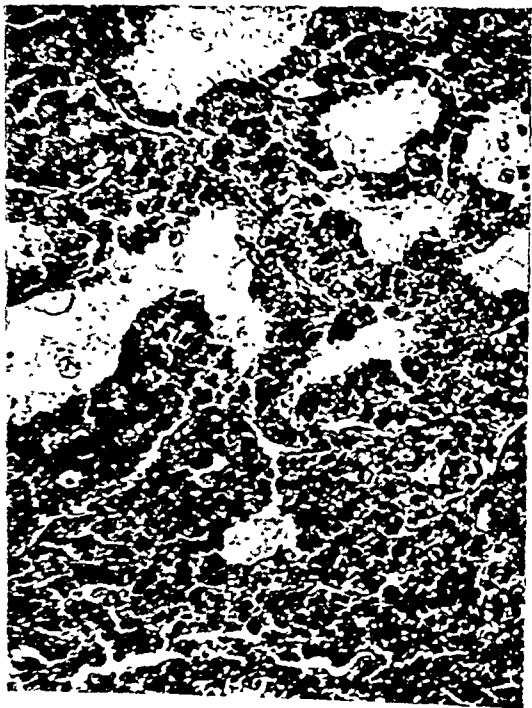
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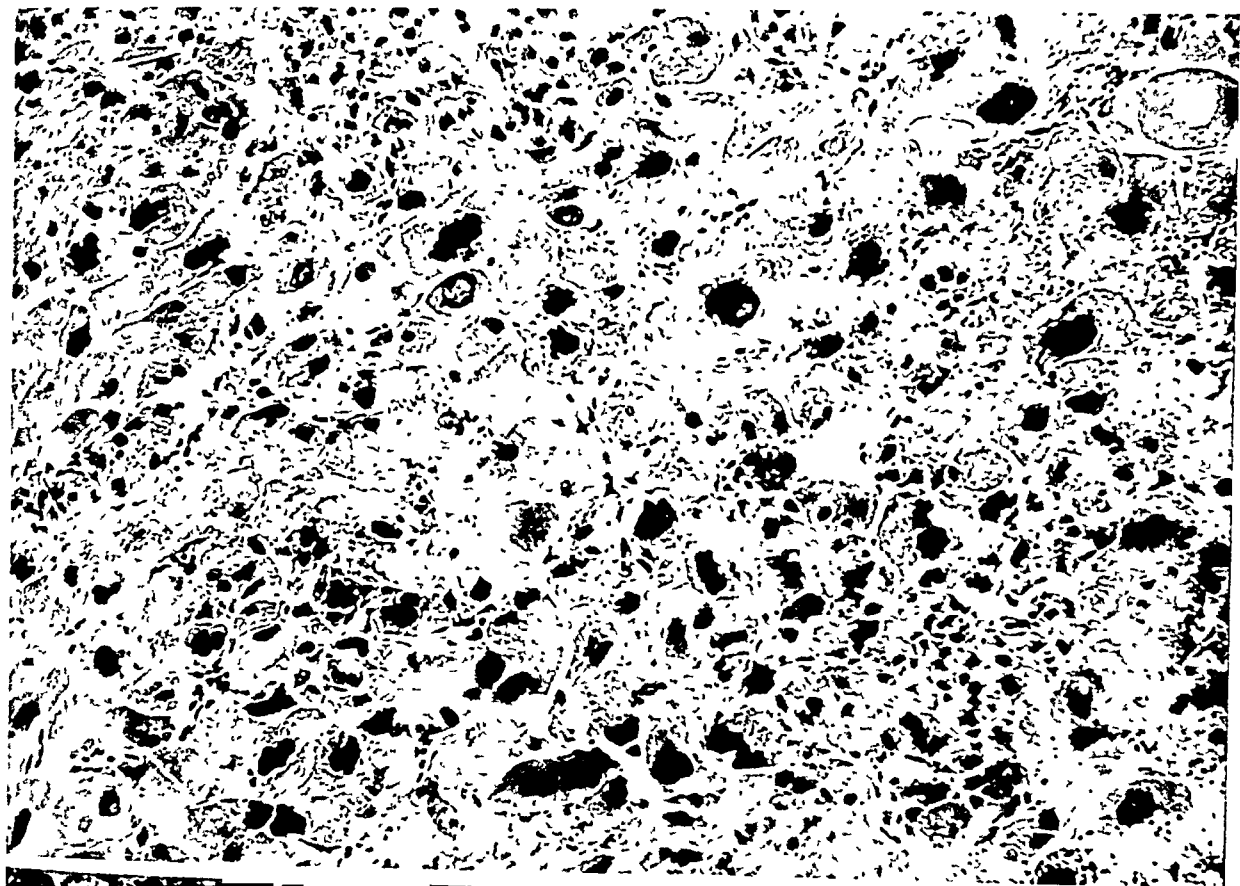
Neumann

Primary Carcinoma of the Liver

PLATE 162

FIG. 7. Metastatic hepatoma in a vertebra. Marked anaplasia of tumor cells. There are slender clefts lined with small, dark nuclei between large neoplastic cells.

FIG. 8. Tumor thrombus adjacent to metastatic growth in vertebral column.



Neumann

Primary Carcinoma of the Liver

BRONCHIOLAR ORIGIN OF "ALVEOLAR CELL TUMOR" OF THE LUNG *

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While in most primary carcinomas of the lung a bronchial origin is easily established, there are occasional cases in which, in spite of a careful search, the point of origin cannot be located. The majority of these, in both the distribution of the tumor and its microscopic appearance, resemble the ordinary bronchogenic variety of carcinoma. A few, however, have a miliary or lobar distribution; infrequently metastasize to distant organs and microscopically are composed of cuboidal or columnar cells lining the alveolar septa. It is this latter group which has been the subject of many previous presentations, under a variety of names, but always with the idea that the primary foci are the septal cells lining the pulmonary alveoli. Recently, Neubuerger and Geever¹ collected from the literature 25 cases of "true alveolar cell tumor" and 15 others which were controversial. Since their publication there have been at least 4 additional cases reported.

Because of the increasing number of these reports,²⁻⁵ it was thought pertinent to draw attention once more to the fact that there is still no convincing evidence that primary pulmonary carcinoma can arise in the alveoli and that all such tumors probably originate in the mucosa of the bronchi and bronchioles. The present report will concern itself with (1) a short summary of the recent views on the status of an alveolar epithelium, (2) the genesis of regenerated alveolar epithelium and (3) a presentation of 6 cases of primary carcinoma of the lung. These were selected from a study of 90 cases which were encountered in the last 6500 necropsies performed at the Jefferson Medical College Hospital. The first 3 to be described meet all the criteria designated as necessary for the diagnosis of an alveolar cell tumor. The remaining 3 cases are typical bronchogenic carcinomas but contain some areas which microscopically are indistinguishable from areas of the former group.

ALVEOLAR EPITHELIUM

For many years the assumption that pulmonary alveoli are lined with a continuous layer of flattened epithelial cells was left unchallenged. Recently, interest in the subject has been revived and at the present time there is much discussion as to the nature of the lining cells. The current views are (1) that there is a continuous layer of epithelial cells (Bensley and Bensley,⁶ Miller,⁷ Bremer,⁸ Cooper⁹); (2) that the lining cells are epithelial but discontinuous (Palmer,¹⁰

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Macklin,^{11, 12} Ham and Baldwin¹³); (3) that the cells are not epithelial but mesenchymal in origin (Rose,¹⁴ Maximow and Bloom,¹⁵ Fried,^{16, 17} Barnard and Day,¹⁸ Loosli¹⁹); and (4) that there are both epithelial and mesenchymal cells present (Sprunt,²⁰ Ross²¹). Although the problem has been studied from the embryologic, histologic and pathologic standpoints, different observers using the same methods have come to diametrically opposite conclusions. For this reason it would serve no useful purpose to enter into a lengthy discussion of this complex and unsettled problem at the present time. The interested reader may turn to any of the aforementioned authors for a complete review of the various opinions.

REGENERATED ALVEOLAR EPITHELIUM

One of the most conspicuous and consistent findings in any chronic inflammatory or fibrotic process of the lung is the presence of cuboidal epithelium forming a continuous lining of the alveolar septa, or spaces in a fibrous tissue stroma. The histogenesis of this epithelium has two interpretations. The older, and by far the more prevalent, view is that the cells arise from former alveolar epithelium which has now resumed its embryonic appearance. This idea has not only been carried down from textbook to textbook (MacCallum,²² Boyd,²³ Ewing²⁴) but has also been reiterated in many recent publications (Wood,⁴ Sprunt,²⁰ Klotz,²⁵ Neubuerger²⁶). Currently it has been discussed at length and rigorously supported by Bell²⁷ and Geever, Neubuerger and Davis.²⁸ The second view is that these cells do not originate from the septal cells but that they are outgrowths of the basal cells of the bronchiolar mucous membrane. Although this idea was voiced by Weller²⁹ in 1929, and described more fully by Fried¹⁶ in 1931, it seems to have been overlooked by most authors.

In an effort to establish the histogenesis of these regenerated cells, a detailed review was made of 60 bronchiectatic lungs together with miscellaneous cases of tuberculosis, organizing pneumonia, interstitial pneumonia and lipid pneumonia. It is believed that cases of bronchiectasis are particularly adapted for this study because the bronchi and bronchioles are continually irritated by chronic inflammation and therefore have a great opportunity to proliferate. Such was found to be the case in almost every lung examined, and since the findings were so consistent they will be considered here. The two most important and constantly observed changes which have a bearing on the problem at hand were (1) the frequent occurrence of metaplasia of the bronchial mucosa to a transitional or squamous cell type, and (2) the presence of varying amounts of granulation or fibrous tissue which consistently surrounded the involved smaller bronchi and their terminal

ramifications, and the gradual merging of this tissue with the adjoining thickened alveolar septa. Throughout these areas, regular, low cuboidal or even attenuated epithelium lined the alveoli and the spaces within the granulation and fibrous tissue. When enough consecutive sections were made, these lining cells were seen to originate in the mucosa of the bronchioles. Most frequently the regular ciliated bronchiolar epithelium ended abruptly, leaving the basal cells to continue out in a linear arrangement into the adjoining tissue and alveoli (Fig. 1). Less frequently the ciliated mucosa was everywhere intact but focally there were collections of proliferated basal cells. These sent out strands of similar cells which later bifurcated into two limbs, and lined spaces in the surrounding fibrous tissue and, beyond this, the alveoli. In either instance the extensions of basal cells from the bronchioles varied. Occasionally the limbs were short, lined only a small portion of the tissue space or alveolus, and then ended abruptly. More frequently, if several sections were cut from the same block, they could be traced without interruption across several microscopic fields. In all cases the regenerated alveolar epithelium had the same morphologic appearance as did the basal cells of the bronchial and bronchiolar mucosa.

To corroborate, on the other hand, the more prevalent assumption that the regenerated epithelium arises from septal cells, an effort was made to demonstrate a gradual attenuation of the cuboidal cells to form ultimately a blending with the normal inner surface of the alveolar wall, or, to find a transition between the newly formed cells and the phagocytes within the alveolar spaces. Nowhere could such relationships be satisfactorily demonstrated. Furthermore, since preoperatively lipiodol was instilled into all of the lungs, there were frequently seen large macrophages whose cytoplasm was distended with ingested oil (Fig. 2). In many instances these lipophages completely filled the alveoli lined by regenerated cuboidal cells and yet none of the latter showed any evidence of phagocytosis. If regenerated alveolar epithelium arises from septal cells, and since septal cells are known to be phagocytic, one would also expect the regenerated cells to show at least some degree of phagocytosis. Thus it seems that all available evidence substantiates the supposition that the source of the regenerated alveolar epithelium is the basal cell of the bronchiole and not the pre-existing septal cell which has now resumed its embryonic appearance.

PRESENTATION OF CASES

Cases Fulfilling the Criteria for Alveolar Cell Tumor

Case 1. A white woman, 50 years old, was admitted to the hospital *in extremis* and died within half an hour. Six months previously she had developed a sudden pain in the chest. This was followed by tightness across the entire thorax, a

hacking, dry cough and later increasing dyspnea. A physical examination was not performed.

At necropsy there were hemorrhagic effusions into the right pleural cavity and the pericardial cavity, and bilateral fibrous and fibrinous pleural adhesions. The entire right lung was gray and diffusely consolidated. Immediately beneath the pleura there were numerous flat, circumscribed or confluent gray nodules measuring 1 to 2 mm. deep and as much as 5 mm. across. Cut surfaces disclosed a homogeneous gray appearance broken only by maplike lines composed apparently of thickened septa. In the medial portion of the upper lobe there was an area of beginning necrosis, 2 cm. in diameter. The left lung contained numerous circumscribed and confluent tumor nodules, measuring as much as 2 cm. in diameter, evenly distributed throughout the parenchyma. A careful examination of the trachea and bronchi disclosed no primary tumor. There were metastases to the mediastinal lymph nodes and liver.

Microscopic sections from each lung were similar. The alveolar septa were slightly thickened because of capillary engorgement or early fibrosis (Fig. 3). Most of the alveoli were partially or completely lined with one to three layers of cuboidal or columnar cells. Although generally these cells were closely adherent to the underlying septa, occasionally there were empty spaces between the lining cells and alveolar walls, while rarely the septa were completely bare and tumor cells were irregularly scattered in the alveolar spaces. The cytoplasm of the tumor cells was always dark-pink-staining and abundant. Occasionally it contained droplets of secretion. The nuclei were either round, oval and of uniform appearance, or showed great variations in shape, size and intensity of staining. Giant cells with 1 to 3 nuclei were abundant. Tumor cells were regularly found within the peribronchial and particularly the perivascular lymphatic vessels and occasionally within the lumina of the bronchioles. The pericardium, mediastinal lymph nodes, liver, adrenals and vertebral bone marrow showed metastases of columnar or cuboidal cells similar to those described in the lungs.

Case 2. A white woman, 48 years old, complained of a persistent cough following pneumonia 1 year previously. She was bedridden the last 9 months, during which time she developed increasing dyspnea and lost 50 pounds in weight. She was emaciated and showed signs of consolidation of the right lung associated with pleural effusion. Roentgenograms of the chest disclosed a homogeneous density on the right side and numerous areas on the left side which resembled "lobular caseous foci."

At necropsy there were fibrous adhesions in the upper part of the right pleural cavity and serous effusions into its inferior portion and into the pericardial cavity. The entire right lung, and particularly its

medial portion, was diffusely consolidated with grayish white neoplastic tissue in which there were small foci of necrosis. The parenchyma of the left lung was infiltrated with innumerable pinhead-sized, gray, firm tumor nodules. The trachea and bronchi showed no primary tumor. There was cancerous involvement of the mediastinal lymph nodes, pericardium and liver.

Microscopic sections of various portions of the lungs showed moderate thickening and fibrosis of the septa (Fig. 4). Tumor cells regularly lined the alveoli either in a linear or papillary arrangement. The cells were mostly tall cuboidal. Their cytoplasm was pink, abundant and nonvacuolated. The nuclei were usually round or oblong and evenly staining, although hyperchromatism was also occasionally present. Giant cells were sparse. At the junction of cancerous and normal lung tissue the septa were thinner, less fibrotic and more congested. Often tumor cells lined only a portion and one side of an alveolus and then ended abruptly. Tumor cells were not found within the lymphatic vessels or the bronchi. Sections of metastatic lesions were similar with the exception that the fibrous tissue strands between the alveoli were broader and denser than those in the lung.

Case 3. A white woman, 52 years old, well until 6 weeks before admission, developed a dry cough, dyspnea, upper abdominal pain, and nausea and vomiting. There were signs of consolidation over the upper portion of the right lung. A roentgenogram of the chest showed haziness on the right side and miliary shadows resembling tuberculosis on both sides.

Necropsy disclosed fibrous and fibrinous pleural adhesions on the left side. The entire left lung was infiltrated with discrete or coalescing gray tumor nodules measuring from 0.7 to 4.0 cm. in diameter. The right lung was essentially similar with the addition that the upper and middle lobes were gray and diffusely consolidated.

Microscopic sections of various portions of each lung showed a moderate thickening of the septa due to capillary engorgement and fibrosis (Fig. 5). While in some fields tumor cells regularly lined the alveoli, most sections showed considerable sloughing of the cells into the alveolar spaces. The cells were tall columnar and contained abundant, dark pink, nonsecreting cytoplasm. The nuclei were round or oval, uniformly stained and peripherally or centrally placed. The most outstanding feature, however, was that even in grossly normal-appearing portions of the lungs there was not a single field that did not contain small, isolated collections of tumor cells. In many areas there were only a few cells in the center of an alveolus, while in others the septa were partially or completely lined in a regular manner. Another outstanding feature was the presence of tumor cells within lymphatic ves-

sels and bronchioles. Sections of metastatic lesions were essentially the same as those in the lungs.

Bronchogenic Carcinomas Containing Areas of Alveolar Cell Arrangement

Case 4. The patient was a man, 69 years old, who complained of cough and expectoration for 14 months and more recently of increasing dyspnea. He showed limited expansion, impaired percussion and decreased breath sounds over the entire right side of the thorax. A roentgenogram of the chest showed homogeneous opacity on the right side obliterating all pneumonic structures.

Necropsy disclosed bilateral serosanguinous pleural effusions. The right visceral pleura was thickened and studded with numerous gray, firm tumor nodules. There was a firm tumor in the right main bronchus causing wrinkling and puckering of the mucosa over a distance of 3 cm. The left lung contained numerous grayish white nodules measuring as much as 6 mm. in diameter. There were metastases to the mediastinal lymph nodes.

Microscopic sections of the primary lesion in the bronchus and various portions of the lungs showed the following four types of tumor cells with gradations from type to type: (1) anaplastic round, spindle or oval cells; (2) masses and sheets of larger cells resembling epidermoid carcinoma without pearl formation; (3) transition from the latter to a glandular type; and (4) cells showing a distinct alveolar arrangement (Fig. 6). In the latter areas the cells were uniformly cuboidal; contained a moderate amount of pink cytoplasm and regularly lined, thickened, and fibrotic alveolar septa. Frequently there were also cells within the alveolar lumina forming structures not unlike renal glomeruli. Throughout the lungs the peribronchial and perivascular lymphatic vessels were conspicuously distended with tumor cells. Sections of metastatic lesions showed the same pleomorphism as did those of the lungs.

Case 5. A white male, 56 years old, complained of pain in the chest for 9 months, dyspnea for 6 months and numbness in the left hand and back for 3 months. There was dullness over the entire right side of the thorax. A roentgenogram of the chest showed an area of diffuse opacity on the right and collapse of the 10th dorsal vertebra.

Necropsy disclosed complete obliteration of the right pleural cavity with dense fibrous adhesions. The right visceral pleura was nodular, gray, and measured as much as 1 cm. in thickness. The lower portion of the main bronchus to the right lower lobe was thickened with gray, firm tissue. Its distal portion was incorporated in a partially necrotic tumor mass which replaced the greater portion of the lobe. The left

lung contained many gray, shot-like tumor nodules, distributed more abundantly in the peripheral portions of the parenchyma. There were metastases to the mediastinal lymph nodes, liver, ribs and lower thoracic vertebrae.

Microscopic sections of the right bronchus and various portions of the lungs disclosed the following distinct types of tumor with transitions from group to group: (1) anaplastic cells with no definite arrangement; (2) larger cells grouped into masses resembling epidermoid carcinoma without keratinization; and (3) regular cuboidal cells lining normal alveolar septa (Fig. 7). The latter contained a moderate amount of pink, occasionally secreting, cytoplasm. The nuclei were round or oval and showed some hyperchromatism. There were occasional giant cells. At the junctions of normal and neoplastic tissue the alveolar septa were often covered only on one side with tumor cells, while the other side was entirely bare. Frequently, only a part of an alveolus was lined and at this point the cells terminated abruptly. Sections of metastatic foci were composed of anaplastic or stratified squamous epithelium.

Case 6. A white man, 57 years old, complained of pain in his bones and a non-productive cough for 4 months. Breath sounds were increased over the apices of both upper lobes. A roentgenogram of the chest showed areas of increased density at the apices of the lungs, interpreted as tuberculosis.

Necropsy disclosed bilateral apical pleural adhesions and tuberculosis of the underlying lung parenchyma. In addition the upper half of the right upper lobe was almost completely replaced with a grayish white, firm tumor which blended gradually with the adjoining parenchyma. The main bronchus to this lobe was normal but its branches were definitely stenotic as they entered the neoplastic tissue. There were two tumor nodules in the lateral portion of the left lung, and metastases to the lymph nodes, adrenals, liver, bone marrow and kidneys.

Microscopic sections of various portions of the right upper lobe disclosed areas of squamous, cuboidal, or columnar epithelium. Frequently the same field showed two types of cells (Fig. 8). Often one alveolus contained a mass of squamous cells and the adjoining surface of the septum was bare. The opposite surface of the same septum was covered with a single or double row of tall cuboidal or columnar cells. The cytoplasm was deep pink and frequently vacuolated. Many of the nuclei were round or oblong, evenly stained and basilar in position. Others varied markedly in shape and size, showed considerable hyperchromatism and were irregularly arranged. Giant cells were frequent.

The alveolar spaces contained varied amounts of pink or blue mucoid material. Sections of metastatic lesions showed a similar pleomorphism of cells.

DISCUSSION

Since the characteristics of "alveolar cell tumors" are so typically epithelial, most authors have called them carcinomas. Their origin from septal cells is the most obvious explanation, and would be entirely acceptable, were it not for the fact that the genesis of septal cells is so much in doubt. If they were definitely shown to be epithelial, there would be no further controversy, but, since the view that they are mesenchymal is gaining more and more advocates,¹ it is extremely difficult to reconcile the supposition that a mesenchymal cell can give rise to a typical carcinoma. To say simply that the germ cells are not specific and that it is possible for a mesenchymal cell to give rise to tumors with epithelium-like characteristics seems hardly enough. Until, however, the origin of septal cells is settled it is rather purposeless to argue the pros and cons of the genesis of alveolar cell tumor on this basis alone. One must, therefore, turn to other available evidence. This is offered in a consideration of the genesis of regenerated alveolar epithelium and in a study of the pleomorphism of the much more commonly observed bronchogenic carcinoma.

Those authors who believe in an alveolar cell tumor as a separate entity invariably point to the frequency with which regenerated alveolar epithelium is found in a variety of chronic inflammatory and fibrotic processes of the lungs. They state further that these regenerated cells arise from septal cells and that sometimes regeneration proceeds so far that the process might even be considered as cancerous. While it is agreed that alveolar cell tumor and regenerated alveolar epithelium have a common origin, and, in fact, that the former may even be preceded in some instances by the latter, I have failed to find any convincing evidence that the septal cell is the parent cell. On the other hand, the focal proliferations of the basal cells of the bronchi and bronchioles with their extensions into the surrounding tissue; their direct linear continuations with the regenerated alveolar cells; the identical morphologic appearance of the two cells; the failure to demonstrate satisfactory transitions between the regenerated cells and the alveolar phagocytes, on the one hand, and the normal inner surface of the septa, on the other; and finally, the absence of phagocytosis by the regenerated epithelium, all point to an origin from the basal cell of the bronchiolar mucosa. I cannot agree with Geever, Neubuerger and Davis²⁸ when, referring to the downgrowth of bron-

chogenic epithelium, they say that "the cells lining such spaces were high-columnar" On the contrary, in the cases studied here, the cells were invariably low cuboidal and in many instances were even somewhat attenuated. This is well illustrated in the accompanying photomicrograph (Fig. 1). Furthermore, while in this report special reference is made to cases of bronchiectasis, the regenerated cells differed in no way morphologically from the regenerated cells observed in the other pulmonary infections reviewed for this communication.

The polymorphism of bronchogenic carcinoma is well known and has been adequately considered by Fried,¹⁶ Klotz,²⁵ Weller,^{29, 30} Boyd,³¹ and others. The instances of bonified bronchogenic carcinoma recorded in this presentation illustrate several points of interest. In cases 4 and 5 the primary sites were definitely established, and, while in each, many cells were anaplastic and others squamous in formation, there were some areas which were typically alveolar in distribution. This was particularly true of case 5 in which the cells were not only tall cuboidal, and so resembled those in cases 1 and 3, but at the junction of normal and neoplastic tissue they lined the alveolar septa in the same manner as did those in case 2. In each of these, one side of a septum was often covered with tumor cells while the opposite side of the same septum was bare. Frequently, too, the cells lined only the tumor portion of a septum and then ended abruptly as though they did not have time to cover the entire surface. Case 4 was included in this report because, while the cells did not resemble those in the first three cases, there are nevertheless recorded instances of alveolar cell tumor in man in which the cells are somewhat lower and in which they are often so arranged as to resemble renal glomeruli. Finally, case 6 illustrates (1) that a primary focus is not always located definitely even in an otherwise typical bronchogenic carcinoma (although the bronchi to the upper lobe were unquestionably stenotic), and (2) the close association of different varieties of cells in the same tumor and even in the same microscopic fields. More specifically, it showed alveoli filled with squamous cells and bare adjoining septa, while the opposite sides of the same septa were lined, not with squamous cells, but with cuboidal cells of exactly the same appearance as those found in a typical alveolar cell tumor.

One of the chief objections to the supposition that alveolar cell tumors arise in the bronchioles has been the failure to locate the site of origin. This, however, is not surprising for, by the time the tumor has reached a size to cause death, such a primary focus will have long been overgrown by neoplastic tissue, or, at least so altered that an

origin from a bronchiole could not be ascertained. To be sure, in case 1 there were several bronchioles whose entire walls were infiltrated with neoplastic tissue yet no one could say positively whether the cancer arose within the bronchiole or infiltrated from without. The answer to this question will lie solely in the examination of very early tumors found incidently at necropsy. The literature contains only one report, that of Ravenna³² in 1909, in which the neoplasm might have been called an alveolar cell tumor had the author not found a gradual transition from normal bronchial epithelium to cancerous tissue, thus establishing a bronchiolar origin.

Although most authors who believe in the existence of an alveolar cell tumor as a separate entity also believe that there are multiple foci of origin, my experience with the cases reviewed for this report makes such a supposition entirely unnecessary. To begin with, it is generally true that carcinomas arise from a single focus and that the remaining growths are secondary. It is also true that often the primary site is extremely small and metastatic lesions so disproportionately large that they first attract attention. If the primary focus in the lung is in the periphery, it may easily be overshadowed by secondary tumors. Since bronchogenic carcinomas ordinarily are considered to arise from one bronchus and the multiple growths throughout the rest of the lungs are considered to be metastatic, why should the same explanation not suffice for carcinomas with an alveolar distribution? In cases 1 and 3, which showed such a distribution of neoplastic cells, many sections disclosed neoplastic tissue within the lymphatic vessels and bronchioles. It is a simple matter for the cells to break through the thin lymphatic walls, or to move peripherally along the lumina of the bronchioles until the air sacs are reached. Such a spread, and particularly by way of the bronchial and bronchiolar lumen, is not limited to tumors with an alveolar distribution, for, in this series of 90 cases, there were many instances in which alveolar spaces contained nests of squamous or anaplastic cells. In fact, in 2 cases which I have recently examined at autopsy, a solid pneumonic spread first attracted attention and was considered as organizing pneumonia, but it was found that a bronchogenic carcinoma was the source of the pneumonic process. Microscopically the alveoli were filled with anaplastic spindle cells but none lined the septa. Apparently the arrangement of neoplastic tissue in the alveoli is dictated by the type of cell present. If the basal cell of the bronchus or bronchiole gives rise to squamous or anaplastic cells, the distribution of these cells will be that of an exudate in acute pneumonia, that is, as clumps in the alveolar spaces and not lining the septa. If, on

the other hand, the basal cell gives rise to columnar or cuboidal cells, then, following the inherent characteristics of these cells to line spaces, they will be regularly distributed along the septa forming the well known alveolar arrangement.

SUMMARY AND CONCLUSIONS

1. A review of the current literature regarding the status of an alveolar lining of the lungs indicates much diversity of opinion. Therefore the possibility of cancer developing from septal cells cannot be either confirmed or denied on this basis alone.

2. Considerable evidence is presented to show that regenerated alveolar epithelium arises not from septal cells but from the basal cells of the bronchioles.

3. On this basis alveolar cell tumors are also considered to arise from the basal cells of the bronchioles and not from septal cells.

4. This is given additional support from a study of the pleomorphism of the more commonly observed bronchogenic carcinoma in which squamous or anaplastic cells and cuboidal or columnar cells are found side by side in the same tumor and even in the same microscopic field.

5. It is believed that the parent cell in all cases of primary carcinoma of the lung is the basal cell of the bronchial or bronchiolar mucosa. The distribution of the subsequent tumor is dependent upon the further differentiation of the cells. If they are anaplastic or squamous, they will be either irregularly distributed throughout the lungs or will occupy the alveolar spaces just as does an inflammatory exudate in pneumonia. If they are cuboidal or columnar, they will regularly line the septa producing the well known alveolar arrangement. While only a few tumors are indisputably of one group or the other, there are many intermediary transitions between the two.

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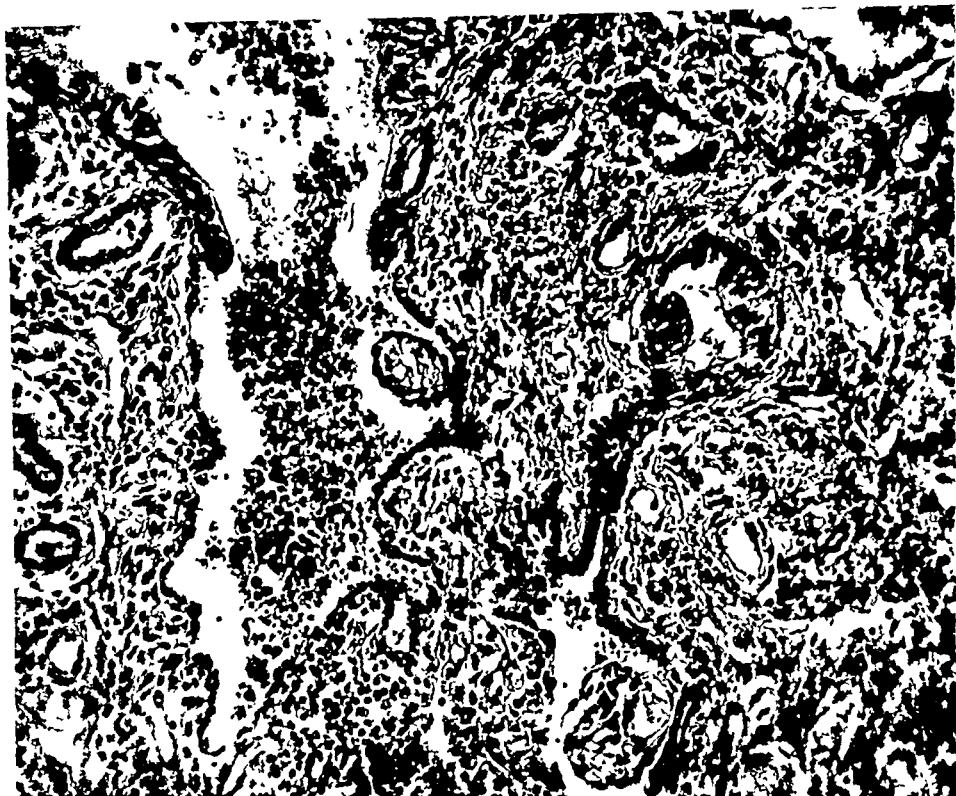
[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 163

- FIG. 1. Section of a bronchiectatic lung showing two bronchioles lined with ciliated columnar epithelium. The larger one, at the left, shows an abrupt termination of the ciliated epithelium and a continuation of the basal cells into the surrounding fibrous tissue. The lumen contains débris and macrophages. The smaller bronchiole, at the right, shows a focal proliferation of basal cells with a cord-like extension into the surrounding tissue and beyond this a bifurcation into two limbs which line a tissue space. $\times 200$.
- FIG. 2. Section of a bronchiectatic lung showing regenerated alveolar cells lining an alveolus. The lumen contains many lipophages. There is no phagocytosis by the regenerated alveolar cells. $\times 400$.

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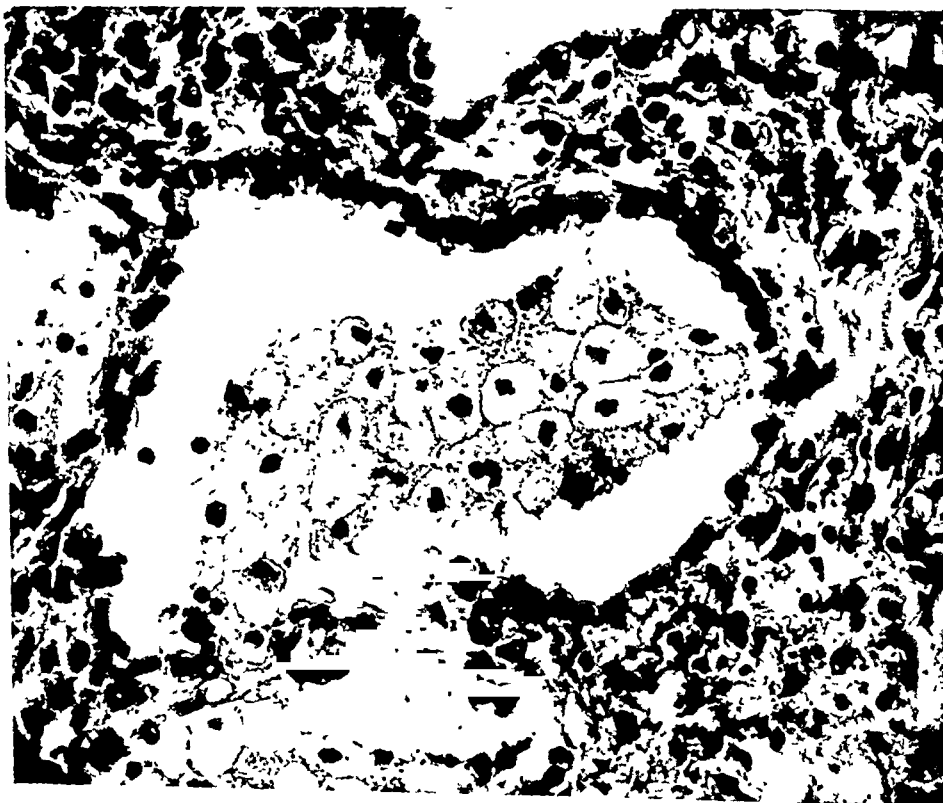
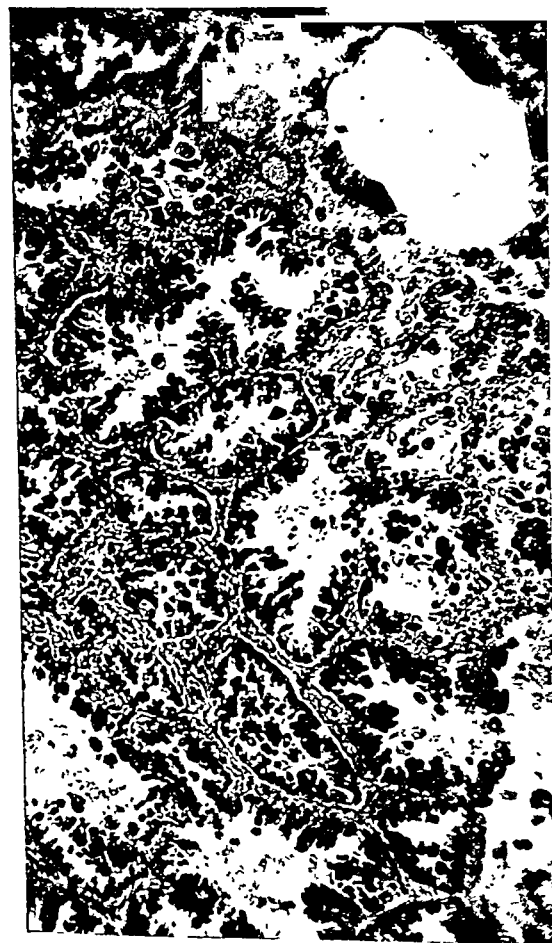
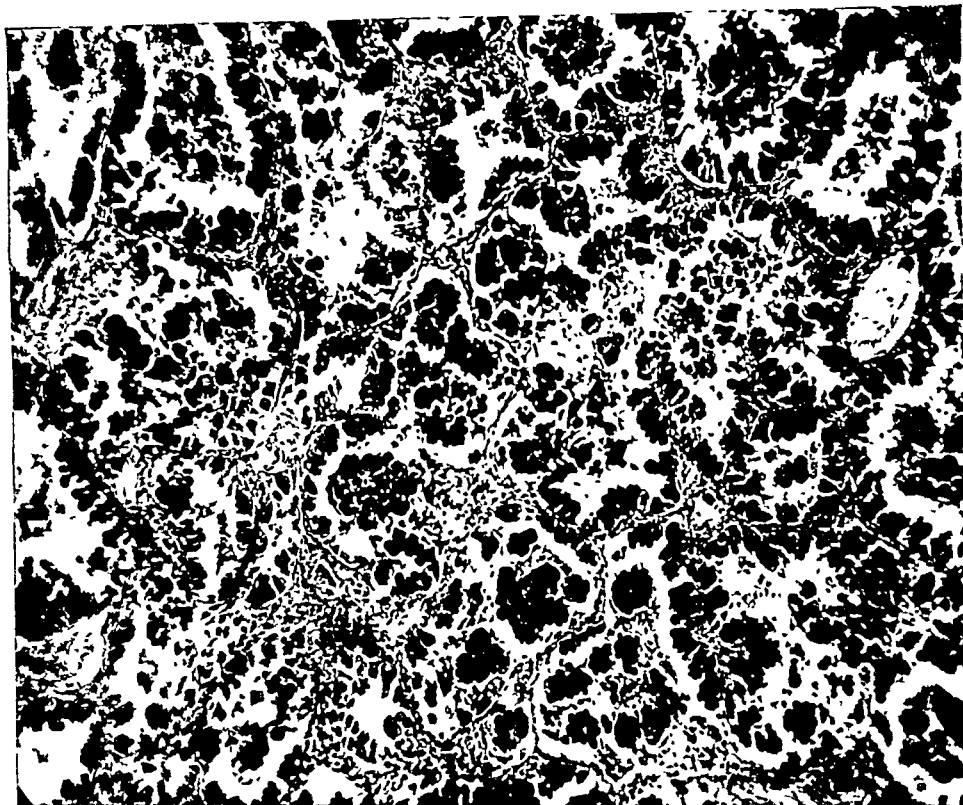


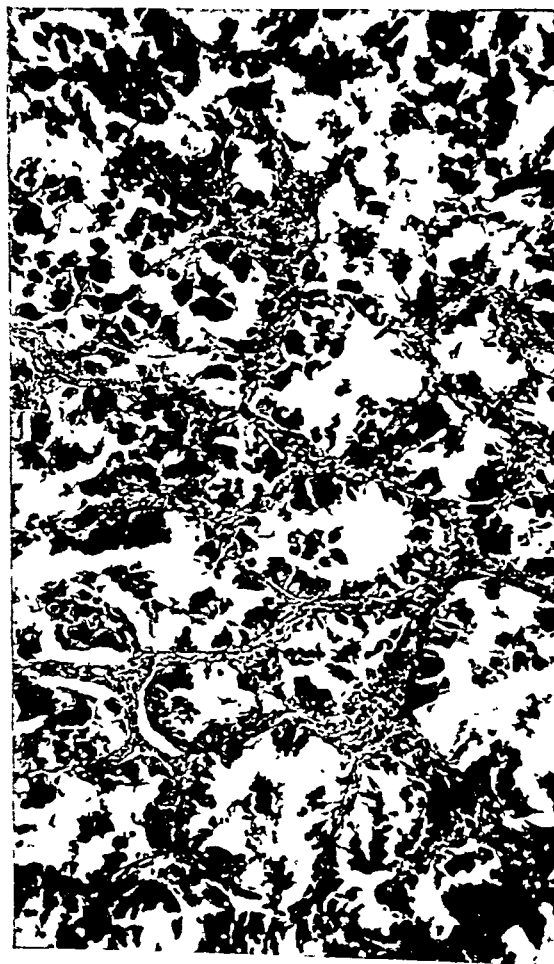
PLATE 164

- FIG. 3. Case 1. Section of a lung showing tall cuboidal or columnar cells regularly lining the alveoli. There is some sloughing of the tumor cells into the alveolar spaces. $\times 100$.
- FIG. 4. Case 2. Section of a lung showing considerable fibrosis of the septa lined with tall cuboidal tumor cells. In the transition from tumor to normal lung the tumor cells cover only a portion of a septum. $\times 100$.
- FIG. 5. Case 3. Section of a lung showing thickened alveoli lined with tall columnar cells. There is considerable sloughing of the cells into the alveolar spaces. $\times 100$.

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Herbut

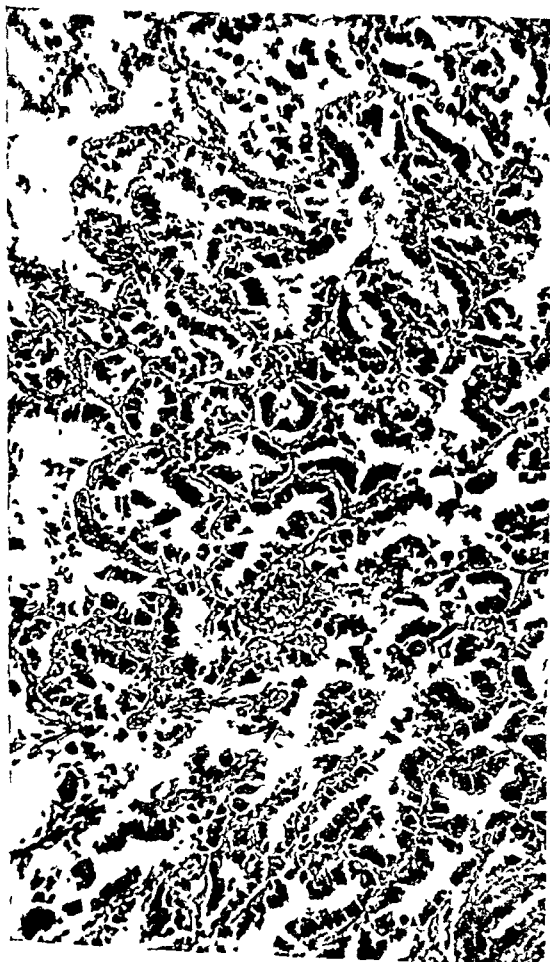
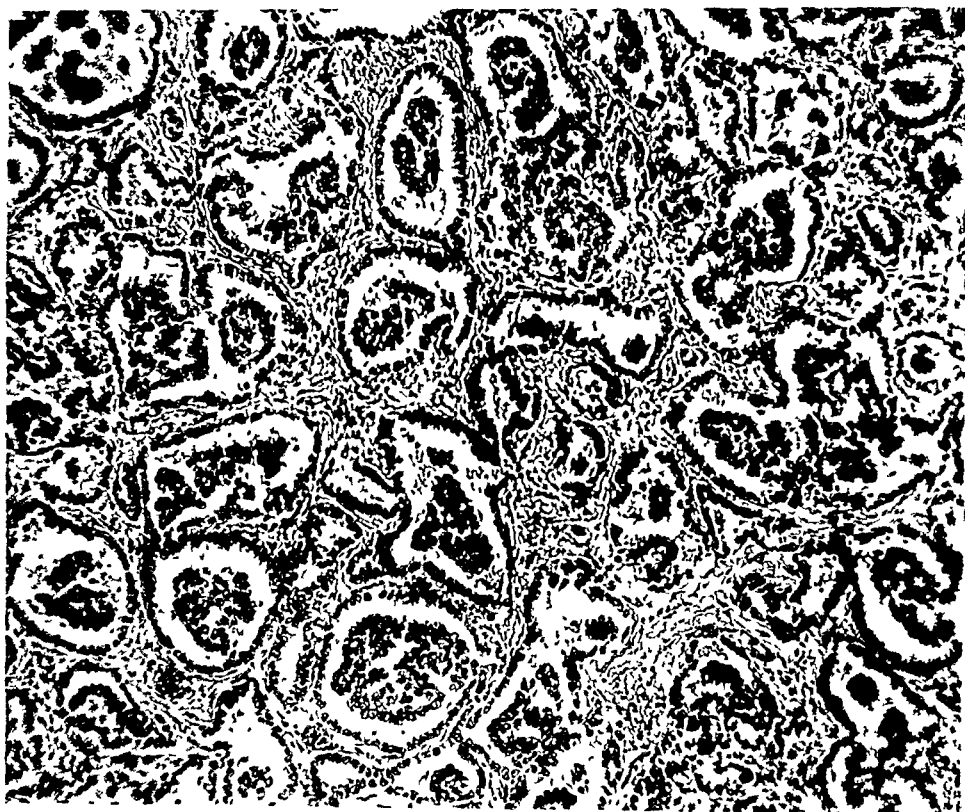


Bronchiolar Origin of "Alveolar Cell Tumor"

PLATE 165

- FIG. 6. Case 4. Section of a lung showing greatly thickened alveolar septa lined with cuboidal cells. There are numerous collections of tumor cells in the lumina, producing structures resembling renal glomeruli. $\times 100$.
- FIG. 7. Case 5. Section of a lung showing tall cuboidal cells lining relatively normal alveolar septa. In the transition from neoplastic to normal tissue in the upper left corner the tumor cells often line only one side of a septum. $\times 100$.
- FIG. 8. Case 6. Section of a lung showing nests of squamous cells filling the alveoli below and columnar cells lining the alveolar septa above. In the transition between the two the same septum in adjoining alveoli is lined on one side with columnar cells while the other side is bare and the lumen is filled with squamous cells. $\times 100$.

6



Herbut



Bronchiolar Origin of "Alveolar Cell Tumor"

PROLIFERATIVE ACTIVITY IN BRUNNER'S GLANDS *

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In a study on Brunner's glands of the duodenum during which more than 1000 duodena were microscopically examined, Robertson¹ came to the conclusion that: "Hardly any more stable and colorless set of tissues can be found in the body. . . . In the presence of acute inflammatory conditions in the mucosa of the duodenum, even with erosions or penetrating ulcers, Brunner's glands are apparently noncombatants. . . . The glands become *spurlos versenkt*." Only twice could evidences of proliferative activity be observed in the region of duodenal ulcers. "These consisted of hyperchromatism of the nuclei, decrease in the cytoplasm and occasional mitosis."

In view of the reactivity shown by other tissues and glands, possessing a higher degree of morphological differentiation, and of Bloom's² statement that in pathological conditions, for instance after local injuries, almost every type of epithelium in the human organism may display a considerable ability for regenerative proliferation, this absence of proliferative activity seemed improbable and we therefore began examining the duodena of our routine autopsy material for the signs of proliferation in Brunner's glands, *i.e.*, mitotic divisions. From the beginning we gained the impression that Brunner's glands are not so dull as Robertson¹ contends and that interesting variations in the cytological details of the glandular epithelium and in the numbers of enterochromaffin cells and oxyphilic cells present in the glands could be observed. After examining a short series of cases our results concerning the proliferative activity of the glands were so different from those of Robertson that we decided to report them.

MATERIAL AND METHODS

During several months the duodenum from every autopsy, which could be performed 1 hour or less after death, was examined. In this way 22 duodena were collected and to these 22 cases 2 earlier examples, in which acute ulcers had been found, were added. The ages of these 24 subjects ranged from 15 months to 71 years. They were all colored people.

Several times the duodenum was removed and fixed immediately after the opening of the abdomen. In most cases Orth's fluid was used for fixation. This fluid is an excellent fixative for the cytological details of the cells of Brunner's glands and for the enterochromaffin cells, the

* Received for publication, November 23, 1943.

granules of which are stained bright yellow, so that they are easily distinguished without special staining methods. Helly's fluid has the same advantages, but paraffin embedding after this fixative causes much shrinking of the tissues.

Péterfi's methylbenzoate-celoidin method for paraffin embedding³ was used and the sections were stained with hematoxylin and azophloxine and orange-eosin-toluidine blue. Only that part of the gland which was lying below the muscularis mucosae was considered and the collecting ducts of the lobuli excluded as much as possible.

REPORTS OF CASES

Case 1

The patient was a colored girl, 5 years old, upon whom autopsy was performed 40 minutes after death. Anatomical diagnoses: meningitis tuberculosa; duodenitis erosiva; melaena.

Microscopical Examination of the Duodenum. In several places there was extensive ulceration which reached to and sometimes into the submucosa. The mucosa between the ulcers showed only moderate inflammation or hyaline necrosis of the tips of some villi. The submucosa was greatly thickened by edema fluid and masses of fibrin, and contained relatively few leukocytes and histiocytes. The walls of several arteries just inside the muscularis had partly necrotic walls. Brunner's glands were present as small lobuli; because of the swelling of the submucosa they occupied only its superficial part. Sometimes they occupied the base of the ulcers. Here as well as in other places, where the overlying mucosa was intact, mitotic divisions were found in the glandular epithelium, though not in great numbers. Here and there leukocytes and desquamated epithelial cells were found in the lumina of the glands.

Case 2

The body was that of a colored male, 37 years old. Autopsy was performed 60 minutes after death. Anatomical diagnoses: cancer of the prostate with metastases in the lungs; bilateral hydronephrosis. The duodenum was without pathological changes.

Microscopical Examination of the Duodenum. The mucosa was without pathological changes. Brunner's glands were unevenly distributed, forming sometimes small lobuli, in other places large accumulations of glandular tissue.

The number of enterochromaffin cells varied from place to place but was not great. The protoplasm of the glandular epithelium was often divided into basal and more superficial parts by a darker staining band of protoplasm.⁴ Many cells contained very minute, pale-staining

granules. Also a narrow band of protoplasm at the base of most cells stained more deeply. An occasional mitosis was found in the glandular epithelium.

Case 3

The patient was a colored female, 68 years old, upon whom autopsy was performed 60 minutes after death. Anatomical diagnoses: contracted kidneys; hypertrophy of the heart; pulmonary infarct; gastric ulcer. The duodenum was without pathological changes.

Microscopical Examination of the Duodenum. The mucosa was normal. In the proximal part of the duodenum there was a large complex of Brunner's glands; in the rest, only small lobuli. The glandular epithelium showed sometimes the same division of its protoplasm as described for case 2. Other cells were filled with minute, pale-staining granules and still others were large and swollen and contained flattened pyknotic nuclei, which were lying at the bases of the cells. There were very few enterochromaffin cells. An occasional mitosis was found in the glandular epithelium.

Case 4

The body was that of a colored male, 60 years old. Autopsy was performed 40 minutes after death. Anatomical diagnoses: coronary sclerosis; extensive fibrosis of the myocardium; ascites; bilateral hydrothorax. The mucous membranes of the stomach and the duodenum appeared to be somewhat swollen.

Microscopical Examination of the Duodenum. The tips of a few villi showed hyaline necrosis; also the scar of a healed, superficial erosion was seen. Brunner's glands were present as large accumulations of glandular tissue. There were very few enterochromaffin cells in the glands. The structure of the glandular epithelium varied widely. Whereas some cells showed the typical aspect of those of mucous glands—large, pale-staining cells with nuclei flattened at the bases of the cells—others were smaller with an oval to rounded nucleus and horizontal strips of dark-staining protoplasm at the base and more or less halfway between the base and the apex of the cell. In the glandular lumina small droplets, possibly of precipitated secretion, were found.

In the glandular epithelium mitotic divisions were very numerous; in some areas 4 to 7 mitoses could be found in one high-power field. They occurred in both types of cells.

Case 5

The patient was a colored male, 55 years old, upon whom autopsy was performed 45 minutes after death. Post-mortem diagnoses: granulating ulcerative colitis; small erosion at the pyloric ring. The duodenum did not show pathological changes.

Microscopical Examination of the Duodenum. The mucosa showed no pathological changes. Brunner's glands were well developed. Be-

tween the tubuli small groups of plasma cells were found. In some places there were many enterochromaffin cells in the glands. The aspect of the glandular epithelium varied as in case 4. An occasional mitosis was found.

Case 6

The body was that of a colored male, 60 years old. Autopsy was performed 60 minutes after death. Anatomical diagnoses: gangrene (diabetic) of both feet; bleeding duodenal ulcer 3 cm. from the pylorus; atrophy of the pancreas; esophagitis.

Microscopical Examination of the Duodenum. Sections from the region between the pylorus and the ulcer showed a few minute spots of hyaline necrosis in the propria mucosae, sometimes still covered with epithelium. Everywhere else the mucosa and the surface epithelium were intact. Brunner's glands were well developed and occupied the whole breadth of the submucosa. The nuclei of the epithelial cells of the glands were oval or rounded and the deep-staining zone of protoplasm at the bases of the cells was well visible. In several places mitotic divisions were found. The ulcer had penetrated into the pancreas. Its edges were steep so that Brunner's glands bordered directly on the necrotic and infiltration zone. Here also mitotic divisions were easily found, sometimes 2 or 3 in one high-power field. The glands retained their typical aspect; atypical formations as in Robertson's¹ Figure 6b were not seen. There was a small acute ulcer in the neighborhood of the larger one; it had penetrated into the submucosa. Brunner's glands bordering on this ulcer also showed a few mitoses.

Case 7

The patient was a colored female, 33 years old, upon whom autopsy was performed 10 minutes after death. Anatomical diagnoses: diffuse serofibrinous peritonitis; postpartum endometritis; necrotic submucous leiomyoma of the uterus. The duodenum was removed immediately after the opening of the abdomen. In the proximal part was a small shallow ulcer.

Microscopical Examination of the Duodenum. The lesions found in the mucosa differed only in extent and degree. In some places only stumps of villi remained. They were covered by epithelium which was lower and stained lighter than usual and did not show a striated border. The normal stroma of the villi was replaced by a hyaline, pink-staining mass, which did not contain nuclei, except those of polymorphonuclear leukocytes. In other places the epithelium had disappeared and hyaline necrosis extended to the muscularis mucosae. The small ulcer had penetrated into the submucosa; it was surrounded by more superficial lesions as described before. The submucosa in the region of the ulcer

was swollen and contained large masses of fibrin and many leukocytes. The normal structures—glands, vessels and nervous tissue—were widely separated; there were but few fibrocytes. Brunner's glands were well developed. In the areas where the erosions and ulcers were found, the glandular epithelium stained more deeply than normal and the cells were smaller than usual. There were few enterochromaffin cells. At some distance from the erosions and from the ulcer, mitoses could be found easily, but in their immediate neighborhood they were present everywhere in great numbers so that sometimes 10 or more mitotic division figures could be counted in one high-power field. Even in glands lying in the base of the ulcer and bordering directly on necrotic tissue, mitoses were found.

Case 8

The body was that of a colored female, 16 years old. Autopsy was performed 40 minutes after death. Anatomical diagnoses: multiple congenital malformations and defects; open ductus Botalli; duodenal ulcer.

Microscopical Examination of the Duodenum. Except for the ulcer, the mucosa was intact. There was diffuse hyperplasia of Brunner's glands. The glandular epithelium had pale-staining protoplasm; the nuclei were flattened at the bases of the cells. The ulcer had penetrated into the pancreas; the edges showed partial epithelialization; there was extensive fibrous reaction. Brunner's glands at the edge of the ulcer showed a few mitotic divisions.

DISCUSSION

As appears from the case reports, we found signs of proliferation in Brunner's glands in 8 of 24, or in one-third of all cases. In cases 1, 6, 7 and 8 there was ulceration of the duodenum and in case 4 a few minute and superficial erosions. Whereas in cases 2, 3, 5 and 8 only a few mitoses were found, they were present in greater numbers in cases 1 and 6, and in cases 4 and 7 they abounded. The few mitoses found in cases 2, 3 and 5 probably represent regeneration after physiological loss of cells, though it is of course also possible that a very slowly developing hyperplasia, caused by some unknown factor, may have been under way. In case 8 the chronicity of the ulcer was perhaps the reason why only a few mitoses were found. Brunner's glands were separated from the areas of necrosis and infiltration by a layer of dense connective tissue and probably an equilibrium between destruction and regeneration of glandular epithelium had been reached. It is difficult to explain the presence of so many mitoses in case 4. It is hard to believe that the few, very small, superficial necroses were the cause. In cases

1, 6 and 7 it was the presence of acute ulceration with the destruction of many cells which caused regenerative proliferation. It should be emphasized that even glands partially surrounded by necrotic tissue showed many mitoses, a phenomenon often observed in the epithelium of the crypts of Lieberkühn in bacillary dysentery. It is interesting to note that in cases 6 and 8, in which the ulcers had penetrated into the pancreas, mitoses were found in the smaller intralobular ducts and the so-called centro-acinar cells.

Though from the statistical point of view our series of cases is very short as compared with Robertson's ¹ 1000 cases, our percentage of cases in which mitoses were found is so high (33 1/3 per cent as compared with 0.2 per cent), and especially the number of mitoses in individual cases is so great, that in our opinion the factor of chance can be excluded. That the difference between our results and those of Robertson is attributable to racial differences, our material being derived exclusively from colored people, is not probable. Nowhere have we found indications in the literature that such differences do exist, though in other respects there are many.⁵ Another possible explanation is that the material used by Robertson was not suitable for these investigations. That this explanation is probably the right one is proved by his photomicrographs. Most of them show well advanced post-mortem changes. We have several times pointed out that such material is not suitable for the finding of mitotic divisions or for delicate histological work.^{6, 7} In morphological pathology, as in every other branch of scientific investigation, only appropriate methods will give good results.

SUMMARY

In 8 of 24 duodena examined microscopically, signs of proliferative activity, *i.e.*, mitotic divisions, were found in Brunner's glands. In 4 cases an occasional mitosis was found, in 2 cases they were in sufficient numbers to be found easily, and in 2 other cases mitotic divisions literally abounded. In the presence of acute inflammatory conditions the epithelium of Brunner's glands reacts in the same way as glandular epithelium in other parts of the body.

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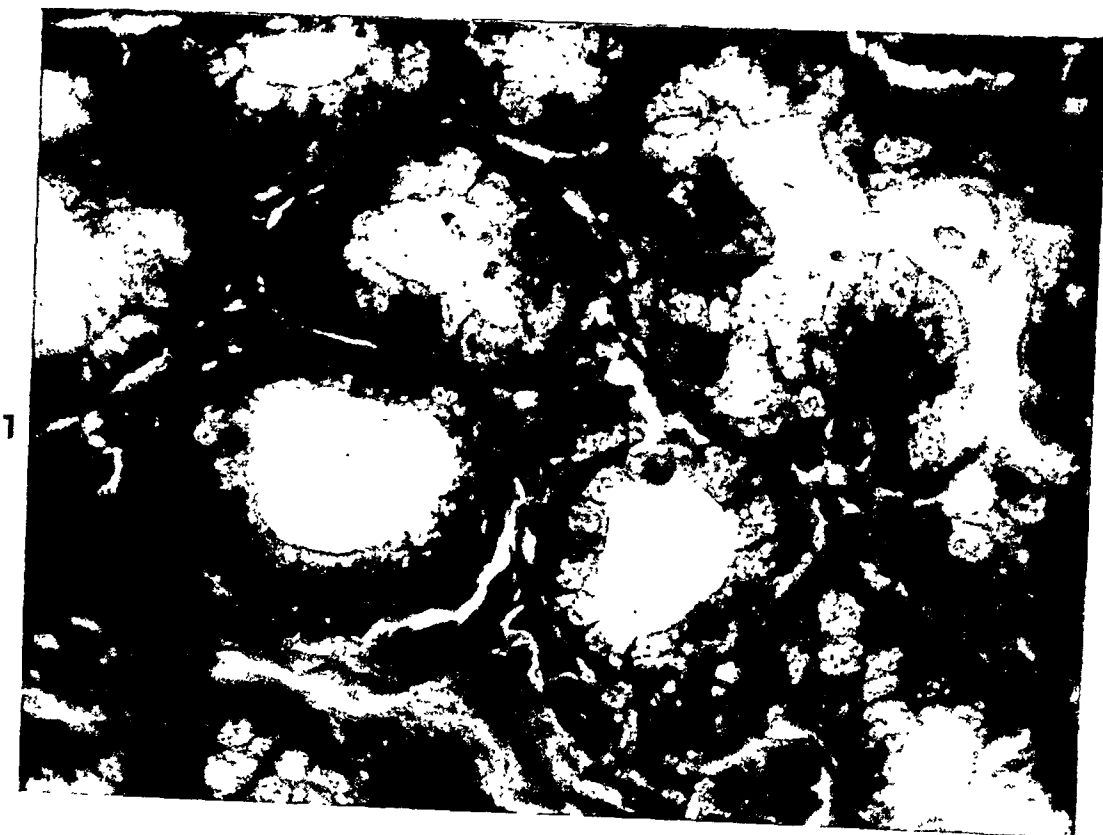
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[*Illustrations follow*]

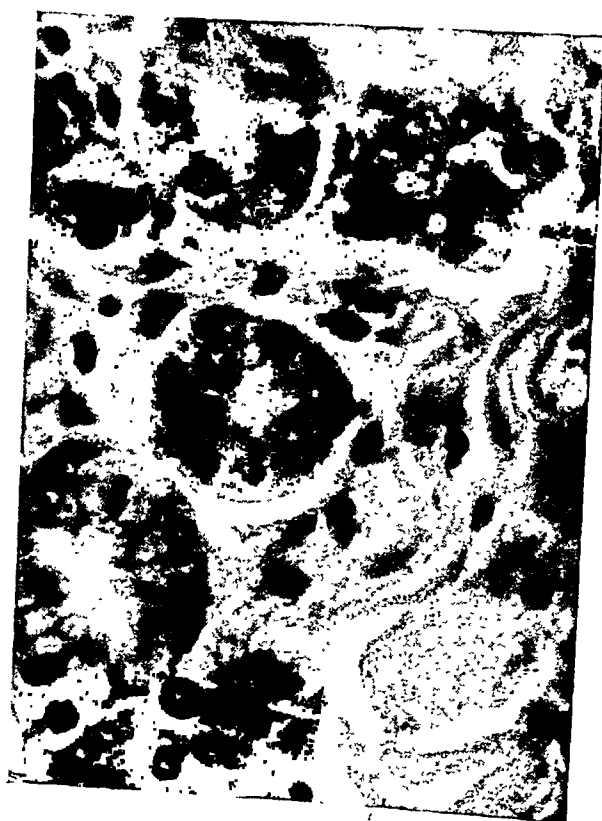
DESCRIPTION OF PLATES

PLATE 166

- FIG. 1. Case 4. Four mitotic figures are present in a relatively small field. Fixation in Orth's fluid. $\times 621$.
- FIG. 2. Case 6. Two mitotic figures are found in the field photographed. Fixation in Bouin-sublimate fluid. $\times 621$.
- FIG. 3. Case 7. Five mitoses are present in the area illustrated. Fixation in Orth's fluid. $\times 621$.



Hartz and van der Sar



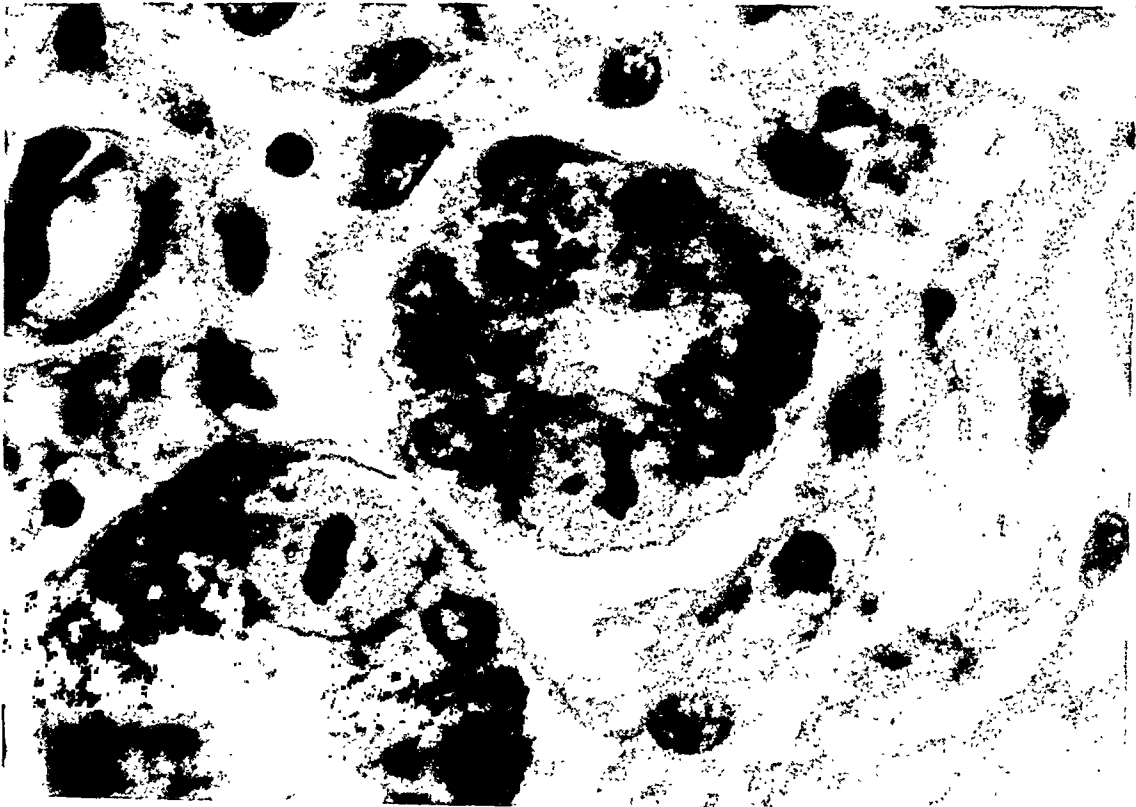
Proliferative Activity in Brunner's Glands

PLATE 167

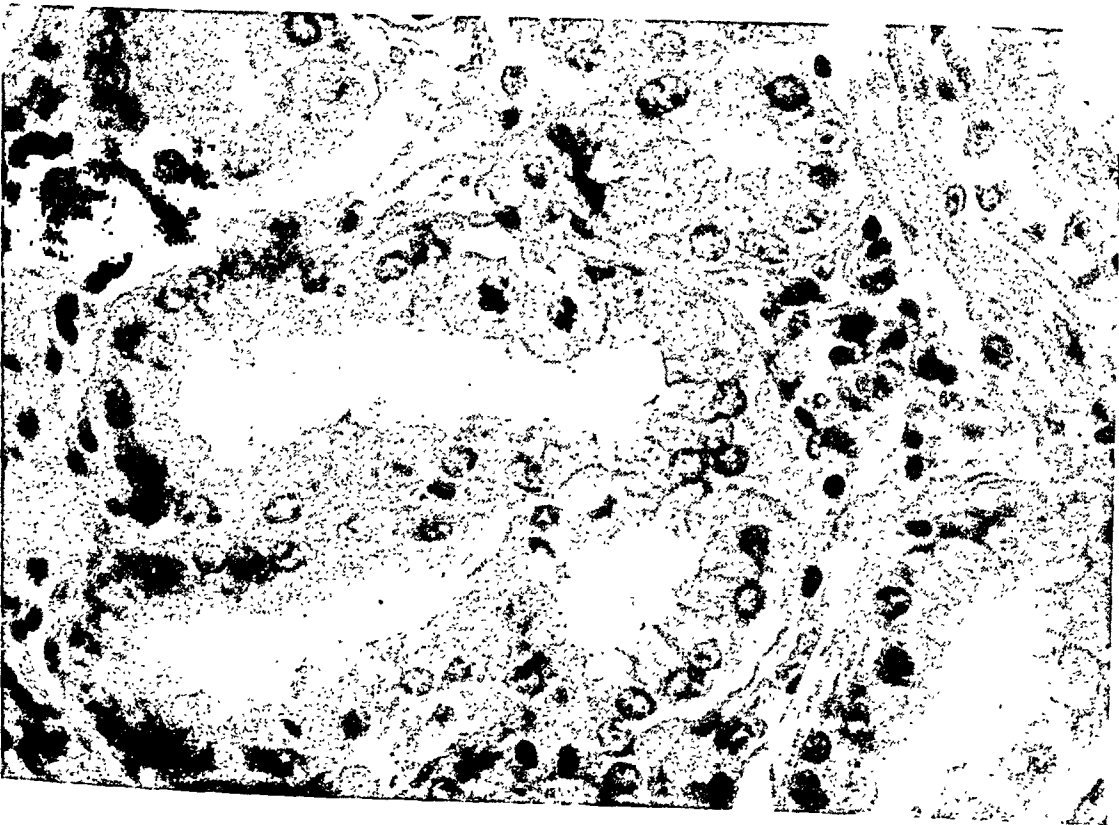
FIG. 4. Case 7. A portion of the same field as in Figure 3 is shown at a higher magnification. $\times 1300$.

FIG. 5. Case 7. Four mitoses are shown. Fixation in Orth's fluid. $\times 621$.

4



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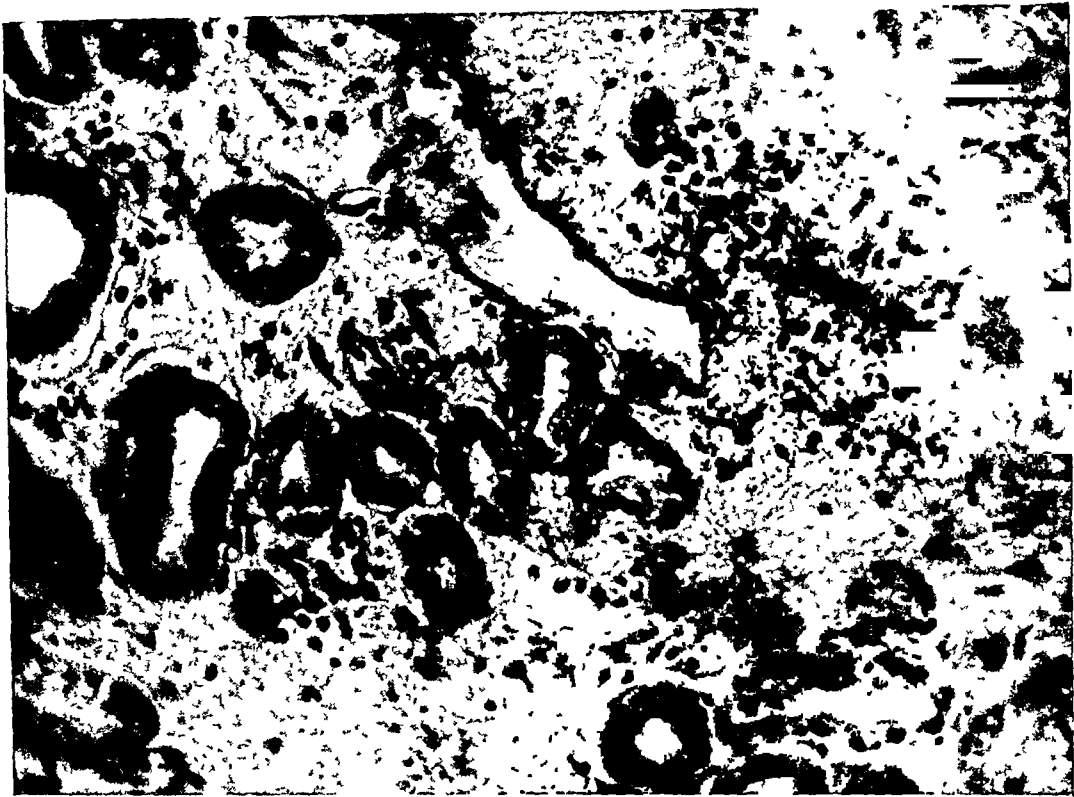
Proliferative Activity in Brunner's Glands

PLATE 168

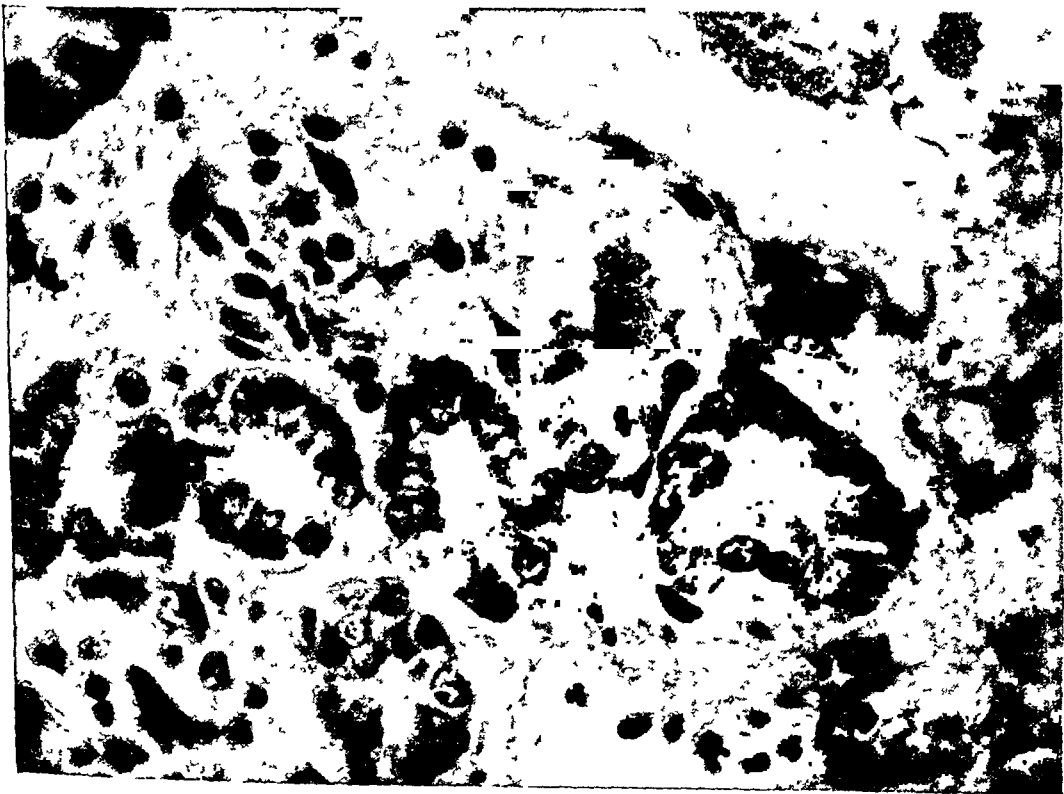
FIG. 6. Case 7. Brunner's glands in the base of an ulcer. Two mitoses are shown in one tubule. Fixation in Orth's fluid. $\times 303$.

FIG. 7. Case 7. A portion of the field of Figure 6 is shown at a higher magnification. The dark-staining zones of the protoplasm of the epithelial cells are shown. $\times 621$.

6



7



Hartz and van der Sar

Proliferative Activity in Brunner's Glands

STUDIES ON THE EARLY CHANGES IN THE LIVERS OF RATS
TREATED WITH VARIOUS TOXIC AGENTS, WITH ESPECIAL
REFERENCE TO THE VASCULAR LESIONS

I. THE HISTOLOGY OF THE RAT'S LIVER IN URETHANE POISONING *

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It is generally accepted that retrogressive changes in the hepatic parenchyma may be caused either by direct action of exogenous or endogenous noxious agents on liver cells, or by insufficient blood supply following the total or partial occlusion of the afferent blood vessels. It has been repeatedly suggested also (Rössle,¹ Schürmann and MacMahon,² Eppinger, Kaunitz and Popper³) that alterations in the structure and function of the lining of the sinusoidal capillaries may lead to pathological changes in the liver parenchyma. Nevertheless, the rôle played by capillary damage in the genesis of lesions of the liver cells is not yet established.

It is certain that the obstruction of an afferent blood vessel can produce necrosis in the area supplied by it. It is conceivable, but it has not been finally demonstrated, that certain endogenous or exogenous toxic substances may interfere with the very specialized metabolic processes taking place in the liver cells and may thus selectively damage them. But it is also highly suggestive that for the life of the liver cell the functional integrity of the lining of the sinusoidal capillaries is essential and that its alterations can provoke damage to the parenchymatous cells.

The following questions present themselves on approaching the problem of the pathogenesis of the retrogressive changes in liver parenchyma induced by various toxic agents:

1. Are there specific liver cell poisons, *i.e.*, substances capable of bringing about damage to the liver cells directly and selectively?
2. Can substances known to be capillary poisons, in addition to the capillary injury, provoke degenerative changes in the liver cells, and, if so, what is the relation between the capillary damage and the degenerative processes in the parenchyma?
3. What is the relative rôle of capillary injury and of primary damage to liver cells in the development of necrobiotic changes in the liver parenchyma resulting from the action of various external and internal noxious agents?

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† Working under The Cancer-Laboratories Fellowship.

The course of the investigations to be described is indicated by the questions outlined above. They represent a comparative study of the action on the liver of poisons of two different types: capillary poisons and so-called liver cell poisons. Final conclusions can be drawn only after comparing and contrasting the mode of action of the various toxic agents to be used. Since histopathogenetic analysis of the action of the diverse toxic substances on liver can effectively be undertaken only before intense damage has developed, our investigations deal mainly with the early stages of the lesions. This, the first paper of a series, is concerned with the changes induced in the liver by urethane.

MATERIAL AND METHODS

Urethane (ethyl carbamate) is a drug with definite vascular action. It produces dilatation of the capillaries, causing an increase in the permeability of the capillary lining (Krogh and Harrop ⁴). According to Landis ⁵ the increased permeability of the capillary wall is not due to the dilatation of the vessel, but in the first place to the toxic effect of urethane on endothelial cells. The toxic effect of urethane has also been demonstrated on *Paramecium caudatum* and on developing eggs of marine animals by Landis, and on fibroblasts in tissue cultures by Geiersbach. ⁶ Little is known of the action of urethane on the liver. Sollmann ⁷ mentioned vacuolization of liver cells after administration of urethane. Whipple and Speed ⁸ found that the administration of large doses of urethane decreased the excretion of phenolphthalein through the bile.

Our observations were made on 25 young albino rats weighing between 70 and 120 gm. The urethane was injected by the intraperitoneal route in a 10 per cent aqueous solution, in single or repeated doses. Animals which received high doses succumbed at varying intervals after injection. The others were sacrificed at specified times.

Pieces of liver were fixed in Carnoy's fluid, Zenker's solution and in a 4 per cent solution of formaldehyde, and blocked in celloidin-paraffin. Sections, 6 μ in thickness, were stained in a variety of ways: hematoxylin and eosin, Giemsa's method, iron-hematoxylin, Mallory's aniline blue collagen stain and Feulgen's method. For identification of fat, frozen sections were stained with Sudan III.

RESULTS

A. EFFECT OF A SINGLE DOSE OF URETHANE

The rats of this series were injected intraperitoneally with doses of 1 to 5 cc. of a 10 per cent solution of urethane per 100 gm. rat. Doses of 3 cc. and more of the 10 per cent solution of urethane will generally

kill the animals in a few minutes. Death may also occasionally occur after doses of 1.5 to 2 cc. In that case the animals die some hours after injection. Animals which did not die were sacrificed 5 to 24 hours after injection.

1. *Rats Which Died 5 Minutes after Administration of 3 to 5 cc. of a 10 Per Cent Urethane Solution.* Macroscopically, the liver appeared enlarged and dark red; its lobular pattern was slightly exaggerated. The outstanding change in the liver revealed by microscopical examination was edema around the portal veins (Fig. 1). The portal veins were surrounded by ring-shaped homogeneous areas which stained uniformly pink with eosin. The accompanying lymph vessels were greatly dilated. The liver cells were pressed back from the vessels by the extravasated fluid. The blood sinusoids in the peripheral parts of the lobules were engorged with red cells and showed no signs of alteration. In the central zone of the lobules the walls of the blood sinusoids were often detached from the liver cell cords. The capillaries lay free in the sinusoidal clefts. The distended pericapillary spaces contained red cells, and sometimes pink granular material. The liver cells were well preserved, but in the central parts of the lobules they showed here and there slight vacuolization.

2. *Rats Which Died 3 Hours after Administration of 1.5 cc. of a 10 Per Cent Urethane Solution.* The damage to the portal veins was more accentuated. There were not only extravasations of plasma, but also of formed elements of the blood (Fig. 2). Large areas of hemorrhage were seen surrounding many of the branches of the portal veins. In the walls of the portal veins numerous red cells were found between the collagen fibers. The changes in the blood sinusoids were similar to those described above and took place always in the central parts of the lobules. The liver cells were definitely vacuolated, especially in the central parts of the lobules, the vacuoles containing only occasional fat droplets; in the periphery the liver cells showed no, or very slight, vacuolization. The nuclei of the liver cells presented no changes.

3. *Rats Which Died 7 Hours after Administration of 1.5 cc. of a 10 Per Cent Urethane Solution.* The portal vessels and larger collecting veins were often surrounded by areas containing edema fluid, granular material and red blood corpuscles (Fig. 3). In addition, there was most intensive damage to the walls of the blood sinusoids, especially in the central parts of the lobules. They were to a great extent separated from the liver cell cords, and the pericapillary spaces contained large quantities of eosinophilic granular material and red blood cells (Fig. 4). The continuity of the capillary wall was frequently interrupted, and its fragments could be seen floating in the sinusoidal

clefts, mixed with the eosinophilic granular masses and red blood cells. The Kupffer cells were frequently detached and pyknotic. In the zones of the intensive capillary damage, namely, in the central parts of the lobules, the liver cells were finely vacuolated and often dissociated (Fig. 5); but in the periphery they showed no abnormalities.

4. *Rats Sacrificed 5 and 24 Hours after Administration of 1 to 2 cc. of a 10 Per Cent Urethane Solution.* Macroscopically, the liver presented a normal aspect or was slightly congested. Microscopically, the cytoplasm of the liver cells was often vacuolated, the vacuolization being more evident in the central than in the peripheral parts of the lobules. In the livers of animals sacrificed after 24 hours some of the vacuoles contained fat. The blood sinusoids appeared normal; their walls adhered to the liver cell cords. Kupffer cells were sometimes prominent. The walls of the portal veins were often edematous and their lining endothelium was missing in various parts. Only occasionally branches of the portal vein showed ring-shaped hemorrhages.

Summary

Animals dying a few minutes after injection of a single dose of urethane showed extravasation of blood plasma around the branches of the portal veins and marked pericapillary edema. In rats surviving for several hours, damage to the portal veins and blood sinusoids was more marked. The walls of the portal veins were infiltrated with erythrocytes, and extensive extravasation of formed elements of the blood through the vascular walls sometimes occurred. The walls of the blood sinusoids, especially in the central parts of the lobules, were often separated from the liver cell cords and sometimes broken. The pericapillary spaces often contained granular material and red blood cells. The liver cells, especially in the central parts of the lobules, showed vacuolization and were sometimes dissociated; in the periphery they showed very slight changes or none. Rats sacrificed after a single nonlethal dose of urethane showed changes of the same type, but much less pronounced.

B. EFFECT OF REPEATED ADMINISTRATION OF URETHANE IN INCREASING DOSES

A 10 per cent urethane solution was used; the beginning dose was 0.5 cc.; the dose was increased daily by 0.1 cc. until death occurred. The animals died after 4 to 14 injections.

Macroscopically, the livers of animals in this series were slightly enlarged and showed congestion. Microscopically, the changes of the portal veins in the livers of animals dying after 4 to 5 days were, in

comparison to the changes described above, not very marked and consisted of mild edema and slight thickening and homogenization of the vessel wall. Occasionally the intimal endothelium was absent, and small denuded areas were found. Extravasation of formed elements of the blood occurred only seldom. There were but very slight changes in the blood sinusoids. They were generally engorged with red blood cells; their walls almost everywhere were well preserved and closely applied to the liver cell cords. The Kupffer cells were prominent; their protoplasm was often markedly eosinophilic and contained numerous chromatin clumps. The liver cells were often vacuolated, particularly in the central parts of the lobules. The presence of fat in the vacuoles generally could not be demonstrated. The nuclei of liver cells were very variable in size; binuclear cells were numerous. Mitoses were frequent.

In experiments of longer duration (11 to 14 days) the changes became more accentuated. The outstanding feature of the damage in this stage of urethane poisoning was the pronounced change in the central parts of the lobules (Fig. 6). Here the walls of the blood sinusoids were often detached from the liver cell cords, and their continuity frequently interrupted. The capillary lumina contained either red blood cells or eosinophilic granular material, sometimes also found in the pericapillary spaces. The extravasation of plasma and formed elements of the blood from the capillary spaces led to the formation of blood "lagoons." The Kupffer cells were prominent and frequently detached and laden with yellow pigment, fragments of chromatin and a few red cells. Their protoplasm was often markedly eosinophilic. The liver cells in the central parts of the lobules, in the zones of the most accentuated capillary damage, were markedly dissociated, atrophic, and in some places there was a disappearance of liver cells. They were generally highly vacuolated. The presence of fat could, however, seldom be demonstrated. In the cytoplasm of the liver cells, red blood corpuscles, singly or in groups, could be found, generally enclosed in a vacuole. The conglomerates of blood corpuscles often reached considerable size and then pushed the nuclei of the liver cells aside. In the course of time the red corpuscles became fused, at first into masses of reticular structure in which individual blood corpuscles were still occasionally recognized, and finally into massive hyaline balls (Fig. 7). The liver cells containing erythrocytes were enlarged. The nuclei of the liver cells were generally well preserved; their size was variable; sometimes they were of dense structure and sometimes pale. Mitotic figures were frequent.

In some rats (experiments of 5 days' duration) many liver cells

contained a rounded body lying near the nucleus and staining deep blue with hematoxylin (Fig. 8). The size of these bodies was generally one-fourth to one-half of that of the nucleus. They were sometimes homogeneous; sometimes they showed a dark blue periphery, pale center and a network of granular or threadlike structures. They gave a positive Feulgen reaction. These structures indubitably were remnants of second nuclei—a product of their disintegration. Clara⁹ noted similar findings in the livers of rabbits poisoned with phosphorus. According to Clara the disintegration of one nucleus in binucleated liver cells mediates the re-establishment of the normal nucleus/cytoplasm ratio which had been altered during the process of regeneration.

Summary

Animals receiving repeated and increasing doses of urethane show relatively slight damage to the portal vessels, manifested by mild edema and homogenization of the vessel wall and occasional endothelial lesions. Changes of the blood sinusoids appear only after prolonged administration of the drug and are limited almost entirely to the central parts of the lobules, where the lining of the sinusoidal capillaries is often detached from the liver cells and sometimes broken. The damage of the capillaries leads to more or less extended extravasation of blood in the center of the lobule with formation of blood "lagoons." The liver cells in the zones of the strongest capillary damage are markedly vacuolated, often dissociated, and sometimes there is disappearance of the liver cells. The liver cells may contain red blood cells, generally fused to spherical masses.

DISCUSSION

The outstanding findings in the livers of animals receiving single or repeated doses of urethane are the damage to portal veins and sinusoidal capillaries, manifested by lesions of the vessel walls which become permeable to blood plasma or to the formed elements of the blood according to the degree of damage.

There are, however, not only vascular and capillary lesions, but also alterations of the parenchymal cells. Compared with that of the blood vessels, the damage of the hepatic cells is only of slight degree and is in the first place manifested by intracellular edema (hydropic degeneration); prolonged administration of urethane may lead to atrophy and disappearance of the liver cells. All liver cell changes take place in the central parts of the lobules, *i.e.*, in zones of the most evident capillary damage. In the peripheral region the liver cells are normal. True necrosis of liver cells was in no case observed.

The characteristic feature of the changes in the liver cells in ure-

thane poisoning is the hydropic degeneration. Hydrops of liver cells has been observed in several pathological conditions, particularly in various kinds of poisoning. The opinion has been expressed that this is caused by the intake of fluid by the liver cells, and that this increased intake occurs when the fluid of the blood in unusual quantities and probably of unusual composition passes from blood vessels into the intracellular spaces.

Investigations on perfused liver provide an experimental basis for this view. The endothelial damage taking place during the perfusion inevitably leads to capillary failure followed by extravasation of fluid. The vacuolization of liver cells is the immediate response to this event. Raum¹⁰ has perfused entire animals with 0.6 per cent NaCl solution. After 2½ to 3 hours intense vacuolization of liver cells could be observed. He considered that the vacuolization of liver cells is a reversible phenomenon due to the surplus of fluid offered. Von Skramlik and Hünemann¹¹ perfused isolated livers of dogs with Ringer's solution and observed that 2 hours after the beginning of the experiments the vacuolization of liver cells appears. Detachment of the capillary membrane from the liver cell cords—pericapillary edema—could also be observed. Milletti,¹² in similar experiments, saw the vacuolization of the liver cells as early as 10 minutes after the perfusion had started.

The fact that in urethane poisoning altered liver cells are frequently encountered, which contain erythrocytes or their disintegration products, is further evidence that in the genesis of the parenchymal changes in urethane poisoning the capillary failure plays a rôle. The ingestion of erythrocytes by liver cells is obviously possible only where the elements of the extravasated blood come in direct contact with the parenchymal cells.

Ingestion of the red blood corpuscles by the liver cells was first described in dogs after injection of hemoglobin by Browicz.¹³ Some time later the same phenomenon was reported by Vereecke,¹⁴ whose observations were made on dogs which received injections of curare, distilled water, or peptone. Rössle¹⁵ saw erythrocytes within liver cells in a case of human hemochromatosis. He expressed the belief that there exists an infectious-toxic disturbance of the capillaries leading to changes in the permeability of the capillary wall. This is followed by extravasation of blood corpuscles which then come in direct contact with the parenchymal cells, and become phagocytized by the latter. Heinrichsdorff¹⁶ reported ingestion of red blood corpuscles by liver cells in cases of jaundice. He assumed that in this condition the capillary damage occurs simultaneously with the damage of the liver cells. Gräff¹⁷ described infiltration of liver cells by red blood corpuscles in guinea-pigs poisoned with *Amanita* toxin. Weatherford¹⁸ observed a

similar phenomenon in dogs in anaphylactic shock. He stated that: "The evidences of increase of capillary permeability, disorganization of the sinusoidal endothelium and parenchymatous necroses detailed in severe anaphylactic shock in the dog make it quite possible that erythrocytes may pass either by diapedesis through the endothelium or directly into the injured hepatic cells."

In analyzing the preceding experimental findings, the following statements concerning the correlation of the liver cells and capillary injury in urethane poisoning can be made:

1. The vascular changes in urethane poisoning predominate to a high degree over the parenchymal injuries.

2. Vascular and liver cell changes are correlated temporally and locally. The changes in the parenchymal cells and the vascular injury appear practically at the same time and unmistakable changes in the liver cells occur only in places where the vascular changes are evident.

3. The character of the parenchymal injuries in urethane poisoning definitely indicates that they take place in an internal environment altered by the breakdown of the normal blood-tissue barrier.

The evidences cited, although highly suggestive that parenchymal changes are causally related to vascular damage, are not sufficient to exclude a direct action of urethane on the liver cells. Pending further experiments, any speculation concerning the causal genesis of liver cell damage in urethane poisoning will remain inconclusive.

SUMMARY

The effect of single and multiple injections of urethane on the liver of the white rat has been studied in respect to alterations of parenchymal cells and vascular lesions. Urethane in large amounts produces very pronounced damage of portal veins and of sinusoidal capillaries, which leads to extravasation of plasma and formed elements of the blood through the vessel wall. The changes in the parenchyma are comparatively slight and consist of vacuolization of the liver cells (hydropic degeneration) combined with occasional intake of red cells. After prolonged action of urethane there is atrophy and disappearance of the liver cells in the central parts of the lobule. Although strongly suggesting that the parenchymal lesions are causally dependent upon vascular injury, the evidence obtained was insufficient to exclude a direct action of urethane on liver cells.

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[Illustrations follow]

DESCRIPTION OF PLATES

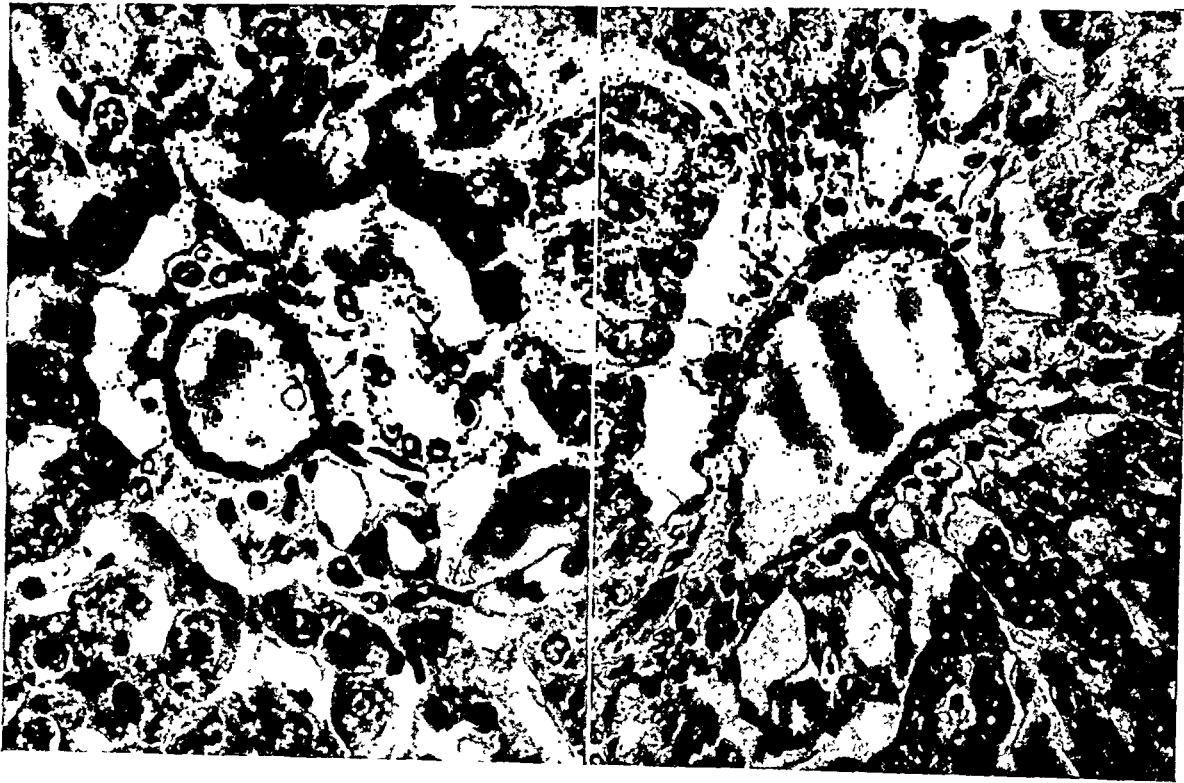
PLATE 169

(All figures taken from hematoxylin and eosin preparations.)

FIG. 1. Two portal veins from rat 60, which died 5 minutes after the administration of 3 cc. of 10 per cent urethane solution, showing the marked edema around the veins. $\times 580$ and $\times 410$.

FIG. 2. From rat 119, which died 3 hours after the administration of 1.5 cc. of 10 per cent urethane solution. Extensive hemorrhage is shown about a portal vein. $\times 190$.

1



2



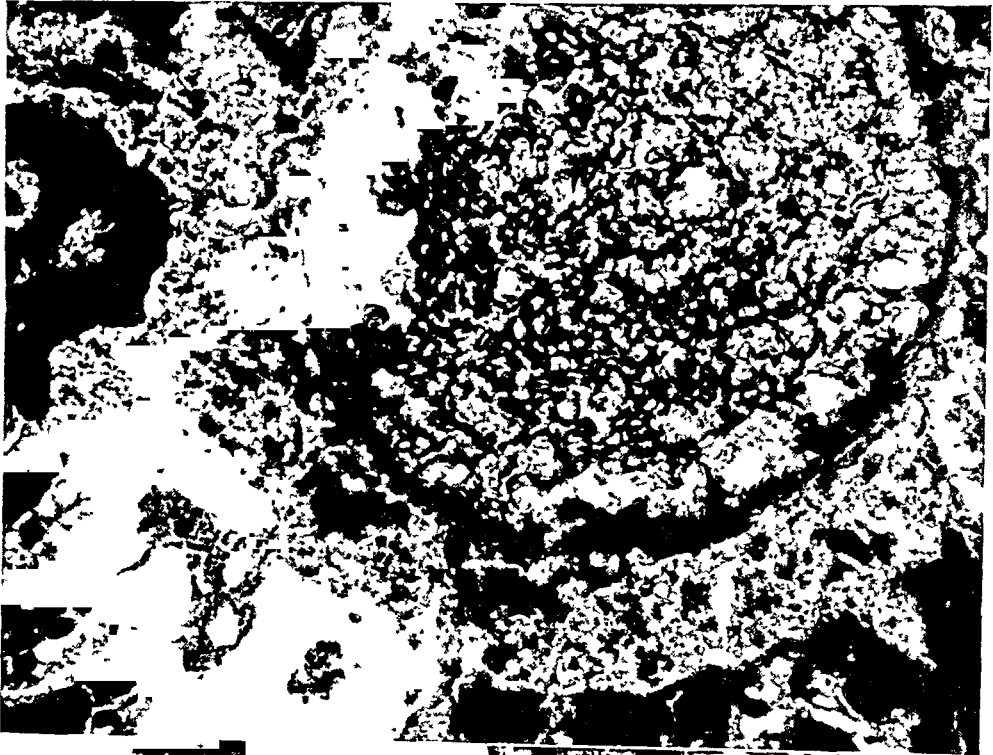
Doljanski and Rosin

Liver in Urethane Poisoning

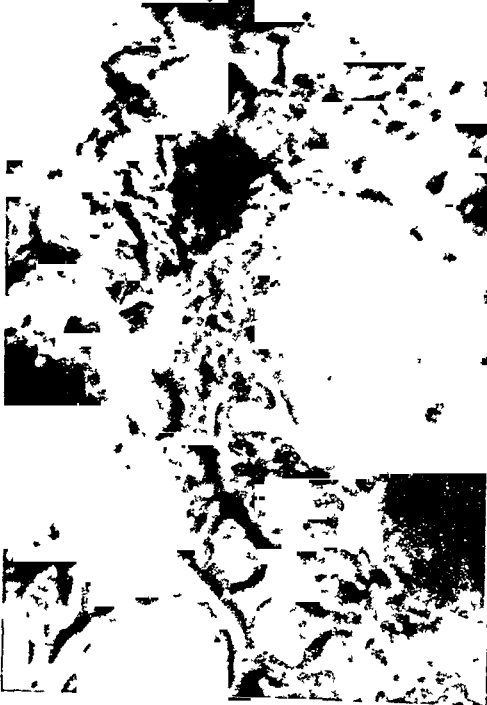
PLATE 170

- FIG. 3. From rat 64, which died 7 hours after the administration of 1.5 cc. of 10 per cent urethane solution. There is an extravasation of both plasma and the formed elements of the blood through the wall of the portal vein. $\times 680$.
- FIG. 4. From the same animal as Figure 3. Granular material is found in the distended pericapillary spaces. $\times 1900$.
- FIG. 5. From the same animal as Figures 3 and 4. Dissociation of liver cells in the central part of the liver lobule. $\times 540$.

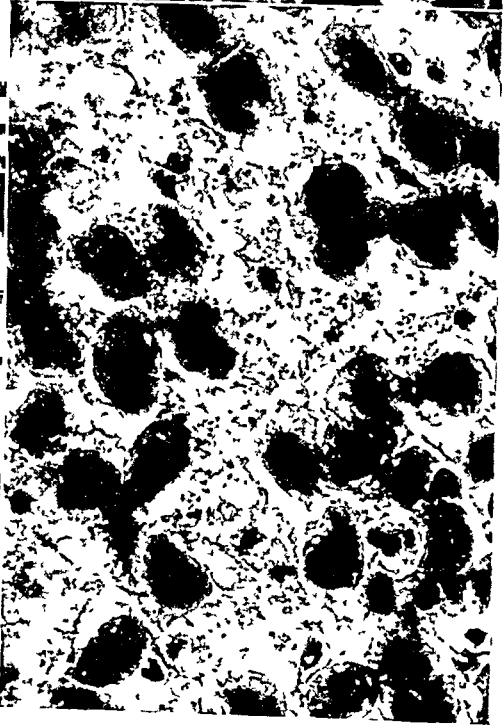
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4



5



Doljanski and Rosin

Liver in Urethane Poisoning

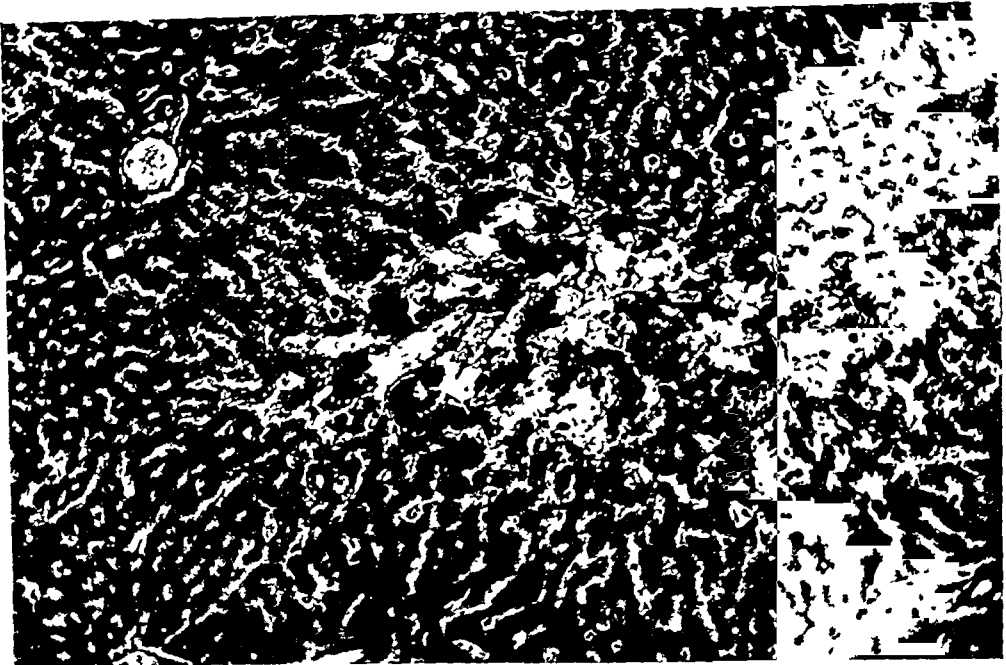
PLATE 171

FIG. 6. From rat 131, which died 13 days after repeated administration of urethane in increasing doses. The changes in the central part of a liver lobule are shown. $\times 120$.

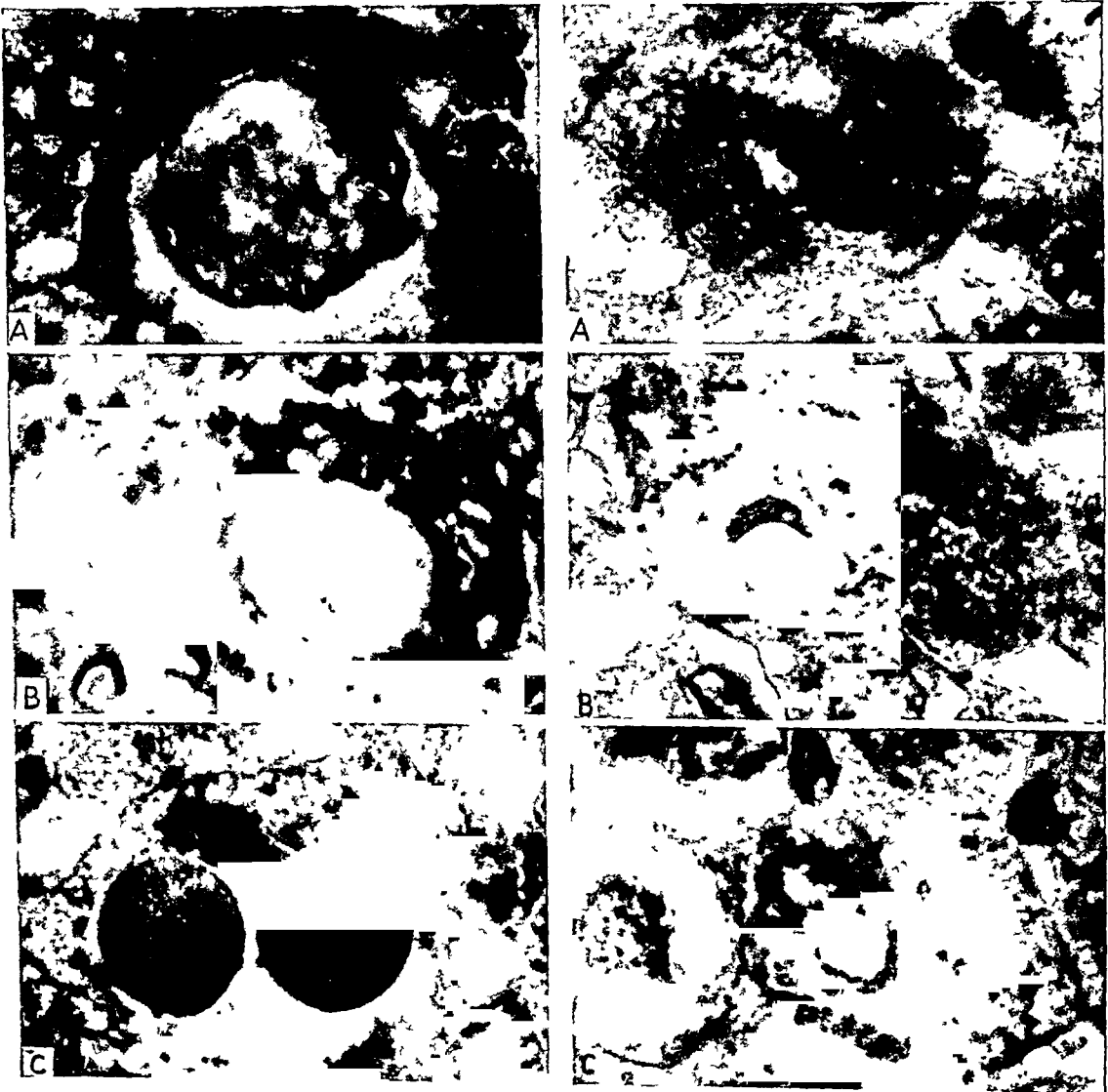
FIG. 7. From rat 130, which died 14 days after the repeated administration of urethane in increasing doses. Conglomerate collections of erythrocytes within liver cells are shown in three different stages of disintegration. $\times 1245$, $\times 1400$, and $\times 1320$, respectively.

FIG. 8. From rat 127, which died 5 days after the repeated administration of urethane in increasing doses. Remnants of second nuclei are shown in three binucleated liver cells. $\times 1320$ for all.

6



7



Doljanski and Rosin

Liver in Urethane Poisoning

STUDIES ON AMEBOID MOTION AND SECRETION OF MOTOR END-PLATES

IV. ANATOMIC EFFECTS OF POLIOMYELITIS ON THE NEUROMUSCULAR MECHANISM IN THE MONKEY*

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A preliminary report has been made¹ of the observations on the early morphologic disappearance of motor end-plates and early appearance of ephemeral projection masses of gold-staining substance in the striped muscle fiber with, or following shortly after, the onset of paralysis in acute poliomyelitis in the monkey. In previous studies by Landsteiner and Levaditi,² Flexner and Lewis,³ Taylor,⁴ Penfield,⁵ Fairbrother and Hurst,⁶ Hurst,⁷ Covell,⁸ Toomey and Takacs,⁹ Sabin and Olitsky,¹⁰ Goodpasture¹¹ and Howe and Bodian,¹² on the histology of poliomyelitis in the monkey, attention was concentrated on the changes in the central nervous system and on parts of the peripheral nervous system. There have been no studies made of the alterations in the neuromuscular mechanisms. In Hurst's¹³ excellent study on the histology of experimental poliomyelitis in the monkey, his observations on muscle are limited to one statement as follows: "Muscles.—Several cases of sarcosporidiosis were found at autopsy." On the other hand, Hassin¹⁴ detected microscopic alterations in epidemic poliomyelitis (Heine-Medin's disease) in human muscle that he considers more important in explaining the symptoms than the alterations in the central nervous system.

The mechanism of action of the virus of poliomyelitis in producing the disappearance of the motor end-plates is unknown. It is assumed that there is an abnormal explosive discharge of the secretion of hypolemmal axonic substance. This gold-staining substance of the axons of the end-plates is assumed to be projected into the myoplasm of the muscle fiber. For some unknown reason this substance projected from the axons does not normally disperse but agglutinates into masses with the accompanying pathologic changes produced by the virus of poliomyelitis. These masses disappear within the first week after their appearance and are not found in all muscles.

The purpose of this paper is to present the complete photomicro-

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graphic evidence, revealed by the gold method, of the alterations in the motor end-plates during the early stages of experimental poliomyelitis in the monkey. Fortunately, the photographs are clear enough without a long, detailed description of the pathologic changes. The exact and clear presentation of these easily verifiable facts necessitates the large number of photographs.

MATERIALS AND METHODS

The present histopathologic study deals with the results obtained by the intracerebral inoculation of a standard dose of 0.5 cc. of a 5 per cent virulent cord emulsion into 6 monkeys (*Macacus rhesus*). The Armstrong-Lansing strain of poliomyelitis virus was used. Additional studies were made on the changes in the motor end-plates of muscles from 8 monkeys obtained from S. D. Kramer, Michigan Department of Health, Lansing; of muscles from 5 monkeys obtained from J. F. Kessel and F. J. Moore, University of Southern California, Los Angeles; of muscles from 2 monkeys obtained from P. F. Clark and A. F. Rasmussen, University of Wisconsin, Madison, and of muscles from 2 monkeys obtained from H. E. Pearson, School of Public Health, University of Michigan, Ann Arbor. We are deeply indebted to these men for excising the muscles and placing them immediately into bottles surrounded by cracked ice in a thermos jug for shipment by air mail or express to Milwaukee.

It was found by experiment that little or no alteration occurred in the motor end-plates when the muscles were cooled to a temperature of 5 to 8° C. as soon as excised and prior to the onset of rigor mortis. Parts of each muscle were either frozen and sectioned, or fixed and stained by various histologic technics. Changes in fat were studied by osmic acid, Sudan III, and scharlach R, and the neurofibrils by the Bielschowsky method counterstained with iron hematoxylin and van Gieson and with toluidin blue. The best method for the demonstration of the pathologic changes in the anatomic continuity of the epilemmal axon, hypolemmal axons that constitute the motor end-plates, and the organization of a striped muscle fiber was a modified gold method followed by careful teasing of small pieces (2 by 5 mm.) of the impregnated muscle. This report will be limited to the findings obtained by the gold method. This Ranvier gold chloride method was modified by Wilkinson¹⁵ and by me¹⁶ and will not be described in detail in this paper.

The following brief protocols are typical:

Monkey 53 (Marquette Series)

April 19, 1943. Inoculated intracerebrally with 0.5 cc. of virulent cord emulsion of the Armstrong-Lansing strain.

- April 23, 1943. Rise of temperature.
 April 26, 1943. Complete quadriplegia; etherized; muscles immediately excised and run through gold technic.

Monkey 54 (Marquette Series)

- April 19, 1943. Inoculated intracerebrally with the Armstrong-Lansing strain.
 April 25, 1943. Rise of temperature.
 April 27, 1943. Fine general tremor of weakened muscles of lower extremities and paralysis of those of the upper extremities.
 April 28, 1943. Complete paralysis of arms, legs and trunk. Difficulty in respiration. Killed with nembutal. Muscles immediately excised and run through gold technic.

Monkey 490 (Kramer's Series)

- Feb. 17, 1943. Inoculated intracerebrally with the Armstrong-Lansing strain.
 Feb. 24, 1943. Rise of temperature.
 Feb. 27, 1943. Weakness of right forelimb.
 Mar. 3, 1943. Complete paralysis of arms and partial paralysis of legs. Exsanguination under chloroform for cardiac puncture. Muscles excised immediately and placed in bottles within iced thermos jug and shipped by air express.
 Mar. 4, 1943. Muscles received and run through gold technic.

Monkey C-89 (Clark's Series)

- Feb. 6, 1943. Inoculated intracerebrally with the Kessel's McK. strain.
 Feb. 18, 1943. Ataxia and tremors.
 Feb. 19, 1943. Marked general paresis.
 Feb. 20, 1943. Complete flaccid paralysis of arms, legs and trunk. Etherized and exsanguinated. Muscles immediately excised and placed in bottles within iced thermos jug.
 Feb. 21, 1943. Muscles received by express and run through gold chloride technic.

Monkey K-334 (Pearson's Series)

- Dec. 18, 1942. Inoculated intraperitoneally and intranasally with the Armstrong-Lansing strain.
 Dec. 21, 1942. Reinoculated intracerebrally and intranasally with a stool suspension.
 Dec. 30, 1942. Complete flaccid paralysis of both legs.
 Dec. 31, 1942. Etherized. Muscles of right lower leg excised and immediately put in bottles within iced thermos jug. Shipped by air express.
 Jan. 2, 1943. Muscles received and run through gold technic.

Monkey K-338 (Pearson's Series)

- April 1, 1943. Inoculated intracerebrally with 2 cc. of a 20 per cent suspension of the Armstrong-Lansing strain.
 April 2, 1943. Rise of temperature to 102.2° F.
 April 18, 1943. Temperature, 106° F.; tremors, ataxia, ruffled fur, paralysis of the right foreleg, weakness of the back and both hind legs.
 April 19, 1943. Temperature, 97.4° F. Complete quadriplegia.
 April 20, 1943. Temperature, 90° F.
 April 21, 1943. Etherized. Muscles immediately excised and put in bottles within iced thermos jug; shipped to Milwaukee by express.
 April 22, 1943. Muscles received and immediately run through the gold chloride technic.

At the autopsies, the usual finding of intense congestion of the meningeal vessels and of the gray matter, especially of the anterior horns of the spinal cord, was noted; on section the nervous tissue was more moist than normal and the cut surface glistening. The affected muscles were intensely hyperemic and more fragile than the normal ones.

Thirty selected muscles from both fore and hind limbs in 2 normal monkeys were prepared by the same gold method applied to the paralyzed muscles and used as controls. More than 3000 teased preparations of the innervation of different muscles were used in this study.

The auriphilous masses of material projected from the degenerating axons were found in certain muscles of 8 of the 23 monkeys studied. These displaced axonic masses were found in greatest abundance in the following muscles: biceps brachii, intercostals, quadriceps extensor femoris, biceps femoris, gastrocnemius, tibialis anterior, sternocleidomastoid, trapezius, pectoralis major and deltoid.

EXPERIMENTAL RESULTS

Histopathology of Motor End-Plates

The motor nerve plates in the relatively normal muscle, quadriceps femoris, in the monkey, varied from the retracted state with wide fronds 15 to 20 μ in diameter (Fig. 1) to the expanded state 30 to 40 μ in diameter. The retracted motor end-plates were usually related to coarse, widely spaced cross striations found in the narrow muscle fibers. There were variations, however, in this relationship. The expanded plates were usually related to fine, closely spaced striations found in the wide muscle fibers. There was a closely graded series of transitional stages in the internal structure of the muscle fibers in relation to motor end-plates of various sizes. The retracted motor end-plate had hypolemmal axon terminals surrounded by an accumulation of Kühne's granules. This mantle of Kühne's granules was either diminished in size or completely depleted in the expanded nerve plates.

With progressive increase of ameboid expansion of the motor nerve plates there was a diminution of Kühne's granules and a corresponding increase in number and fineness of closely spaced cross striations. The strongly contracted muscle fibers had large motor nerve plates with two or more moniliform projections separated by wide spaces. With progressive increase in size of the motor nerve plate and increase of fineness of the dark and light transverse striations, the contracted muscle fiber took a differential stain. This indicated either a physical or chemical change in the contracted muscle fiber. There were many

transitional stages and gradations between the coarsely and finely striated muscle fiber. There was a substantial ameboid protrusion of the processes of the nerve plate in various directions in the muscle substance which increased the surface area of the nerve plate and variability of the muscle striae. This was evidence that during life the muscle striae were not constant and rigid membranes.

In some muscle fibers there was a periodic alternation of fine, closely spaced striations and coarse, widely spaced ones. In other places the muscle substance was coagulated into masses in which no striations were visible with the highest powers of the microscope. This compact muscle substance resembled Zenker's¹⁷ waxy degeneration. From experimental evidence, Wells¹⁸ concluded that these opaque hyaline masses represent a local accumulation of lactic acid. By applying lactic acid to striated muscle *in vitro* and *in vivo* he caused structural changes resembling Zenker's waxy degeneration. The internal structure of the muscle fiber, therefore, appeared to be intimately related to the variable biochemical composition. The variations in the normal structure of the living muscle fiber appeared to be an expression of the changing chemical reactions. There may be a closer association between histologic structure and chemical composition than is now realized.

The differential fiber types were present in the normal muscle (Fig. 1) but they were absent in the paralyzed muscle (Fig. 2). Many of the end-plates on the first day of paralysis were retracted into small ball-like masses (Fig. 2) with shortened axis cylinders and intense affinity for gold. Likewise, on the first day of paralysis, there were a few enlarged granular end-plates that had a weak affinity for gold. Between 20 and 25 per cent of the motor end-plates were absent in the paralyzed muscle on the first day (Fig. 11). Within 2 to 4 days after the onset of paralysis about 50 per cent of the end-plates had disappeared (Figs. 6, 12 to 16, and 27 to 33). During the first 24 hours the paralyzed muscle had definite passive hyperemia of the muscular capillaries and veins. The muscular fibers were prominently identified by the presence of congested intramuscular vessels (Figs. 3 and 4, 7 to 10, and 17). During the first 48 hours the paralyzed muscle had trees of end-plates with variable degrees of retraction and granular fragmentation (Figs. 3 to 5).

Many retracted trees of axons were completely depleted of end-plates by the third or fourth day of paralysis (Fig. 6) and had sharp or bud-like epilemmal terminals in the triceps muscle. The rates of nerve degeneration were unequal in different muscles of the same animal and in different fibers of the same muscle. The weakened biceps

brachii muscle had an innervating tree of retracted ball-like motor end-plates (Fig. 10) whereas the paralyzed triceps muscle had, on the first day of paralysis, an innervating tree with practically complete absence of all of the motor end-plates (Fig. 11).

Observations were made of an unusual histologic condition characterized by masses of gold-staining material closely associated with the degenerating tree of innervation. These masses were located both externally and internally to the muscle fibers (Figs. 12 to 16). They varied in length from 5 to 105 μ . They were found in 8 of the 23 monkeys studied from 1 to 4 days after the onset of paralysis. They were not found after the seventh day of paralysis. The gold-staining masses were found in the following muscles: biceps brachii, intercostals, quadriceps extensor femoris, biceps femoris, gastrocnemius, tibialis anterior, sternocleidomastoid and trapezius. These gold-staining inclusion masses were composed of granules 0.1 to 2 μ and globoid bodies 2 to 4.5 μ in diameter (Figs. 18 to 26). Each of these bodies was frequently surrounded by a clear halo-like space (Fig. 26). In some places these masses were uniformly and densely stained. In others they had a clear-cut arrangement into cross striations, whereas in still others the periphery of the auriphilous masses was indented in a festoon-like manner by the normal cross striations of the muscle fiber. In many places the granules of the gold-staining masses were aligned in a manner corresponding to that of the normal cross striations of the muscle fiber. In other locations the cross striations of the inclusion masses had a periodicity of their own which did not correspond to that of the immediately related cross striations in the muscle fiber.

It is assumed that these gold-staining inclusion masses were projected from the termination of the degenerating axon into the muscle substance. The assumed relationship of these masses to the axonic substance is based upon two histologic facts; namely, (1) the similarity of the staining capacity of the inclusion masses to that of the axon, and (2) the appearance of the inclusion masses out in the muscle substance corresponding in time to the attenuation of the axonic terminals and diminution of their content of gold-staining substance. In other words, these inclusion masses were assumed to represent an abnormal secretion of the substance of the motor end-plate and a failure of normal dispersal of this product of axonic secretion throughout the muscle fiber.

These inclusion masses had a more intense staining capacity for gold than that of the normal cross striations in the muscle fiber. Since Hurst¹³ claimed that he found sporidiosis in some of the muscle fibers

of the monkey, care was taken to differentiate histologically these gold-staining inclusion masses from sporidia. In 18,246 muscle fibers of the left quadriceps extensor femoris muscle (monkey 490, Kramer's series) these inclusion masses were found in 14,164 fibers in close association with the zone of rapidly disintegrating innervation. These inclusion masses had not been found in 30 muscles of 2 normal control monkeys, nor in those examined more than 1 week after the onset of paralysis. These ephemeral inclusion masses at the degenerating myoneural junction appeared to be characteristic, as far as this limited evidence goes, of certain unknown chemical reactions that occur at certain times during the early stages of experimental poliomyelitis within and near the degenerating innervation of muscles in some monkeys. There may be an affinity of the virus of poliomyelitis or its products for acetylcholine or some related substances delivered by the end-plates into the muscle fiber.

The degenerative process resulting in either the diminution or complete depletion of gold-staining substance from within the terminal axons of motor nerves appeared to begin at the end-plates in the muscle fiber and then progressed in a centripetal direction (Figs. 27 to 33). There was first a dissolution of the hypolemmal axons and a related variable quantity of the granules of Kühne that constitute the end-plates. At the beginning the epilemmal axons were engorged, in many places, with gold-staining substance (Figs. 6 and 11) but denuded of end-plates. Within 48 to 96 hours some of the intramuscular nerve trees showed their epilemmal axons with decreased amounts or completely depleted of axonic gold-staining substance. The ghost-like outline of some of the axons had either scattered granules of the fragmented axons or complete absence of granules peripherad, whereas more centrad (Figs. 27 to 33) the same epilemmal axons had a strong affinity for gold because of the persistence of the axonic substance.

There is no adequate chemical explanation as yet for either the morphologic dissolution of the end-plates or the centripetal direction of depletion of the peripheral terminals of the epilemmal axons of their gold-staining substance produced by poliomyelitis. Many experiments were suggested by these findings and more facts must be established before an adequate theory may be advanced to explain these observed facts of the pathology of the motor end-plates.

Passive hyperemia of the capillaries was prominent in some muscles during the pre-paralytic and early paralytic stages of muscle weakness. Each muscle fiber was clearly delimited because of the greatly congested capillaries, the content of which had abnormally increased af-

finity for gold (Figs. 3, 4, 7, 8, 9, and 17). In some places there was a beginning proliferation of the perivascular reticulo-endothelial mesenchymal cells in the weakened muscles. Endothelial vascular sprouts of the beginning of vasculogenesis were observed in some places (Fig. 9).

SUMMARY

1. The early histologic changes that occurred in the neuromuscular mechanism of experimental poliomyelitis in monkeys were studied by the gold method in comparison with the muscles from 2 normal control animals. A quantitative analysis of the anatomic changes was aided by both low-power and high-power photomicrography.

2. The earliest pathologic change was hyperemia and beginning perivascular infiltration of certain areas of the intramuscular blood vessels, which had more granules with strong affinity for gold in the lumen than did the normal. This hyperemia was detected in weakened but nonparalyzed muscles in certain places prior to alterations in the structure of the motor end-plates.

3. On the first day of paralysis some of the end-plates were retracted in ball-like masses and others were hypertrophied and granular. About 20 per cent of the motor plates were absent in the paralyzed muscle on the first day, and within 2 to 4 days about 50 per cent of the end-plates had disappeared. The rates of denervation and degeneration were not only unequal in different muscles of the same animal but in different groups of muscle fibers within the same muscle.

4. Projected masses of gold-staining axonic substance were found in close relationship to the degenerating tree of innervation from 1 to 4 days after the onset of paralysis. They were absent after 7 days of paralysis. They were found in certain muscles of 8 of the 23 monkeys studied. These auriphilous masses were composed of granules and spheroid bodies that varied from 0.1 to 4.5 μ in diameter and in some places were arranged in cross striations which had a more intense affinity for gold than the ordinary cross striations of the muscle fiber. These ephemeral gold-staining masses were not found in 30 muscles of 2 normal control monkeys nor in muscles after 1 week of paralysis. These projected masses of axonic substance at the degenerating neuromuscular mechanism appeared to be characteristic, as far as this limited evidence goes, of certain unknown chemical reactions that occur at certain times during the early stages of experimental poliomyelitis within and near the degenerating innervation of some muscles in some monkeys.

5. The degeneration appeared to begin in the motor end-plates and

then to extend in a centripetal direction through the epilemmal axons in many of the nerve trees observed.

6. The tentative hypothesis is advanced that the histopathologic changes observed at the neuromuscular mechanism during the early stages of poliomyelitis are the result of an abnormal excitation of the secretory mechanism of the motor end-plates which results in the progressive exhaustion of the gold-staining axonic substance leading to denervation at the myoneural junction. This early material exhaustion of the terminals of motor nerves in skeletal muscle by the virus of poliomyelitis will be studied in relation to the chemical secretion of acetylcholine. This experimental study will be extended to include a correlation of the changes in the neuromuscular mechanism with those in the spinal cord and medulla oblongata in the same animal.

I wish to express gratitude to Mr. Leo Massopust, Director of the Department of Art and Photography, for aid with the photomicrographs; to Dr. G. Kasten Tallmadge, Assistant Professor of Anatomy, for reading the manuscript; and to Messrs. Eugene Haushalter, John Schmitz, James Keyes, Joseph Hamel and Robert Jeub for technical aid in the teasing of muscle and nerve plates.

ADDENDUM

Subsequent to the acceptance of this paper for publication evidence has been obtained which supports the statement that metabolic substances such as lactic and other acids may accumulate abnormally during anoxia locally produced in the muscle and thereby destroy the motor end-plates. The abnormal accumulations of ephemeral axonic substances extrinsic to the end-plates undergoing liquefaction are observed in some of the muscle fibers. This is due either to an abnormal permeability of the end-plates and secretion of axonic material or a delay in its dissolution after this material is secreted from nerve to muscle.¹⁹

It has been established that abnormal amounts of lactic acid appear in the blood in hemorrhagic,²⁰ traumatic,²¹ and "gravity"²² shock. The pathology of the end-plates leading to their destruction and the evanescent appearance of axonic nervous material in the muscle during the incipient stages of hemorrhagic shock²³ is quite comparable to that of the early effect of lactic acid and poliomyelitis. Gesell and his colleagues found that lactic acid caused a delay in the destruction of physiologically deposited acetylcholine at the synapses.^{24, 25} Whether or not the abnormal amount of nervous material histologically observed in muscle in poliomyelitis, in the lactic acid series of experiments, and in experimental shock are the morphological expression of

the temporary appearance of, and the delay in, the dissolution of acetylcholine in muscle cannot be answered conclusively at the present time.

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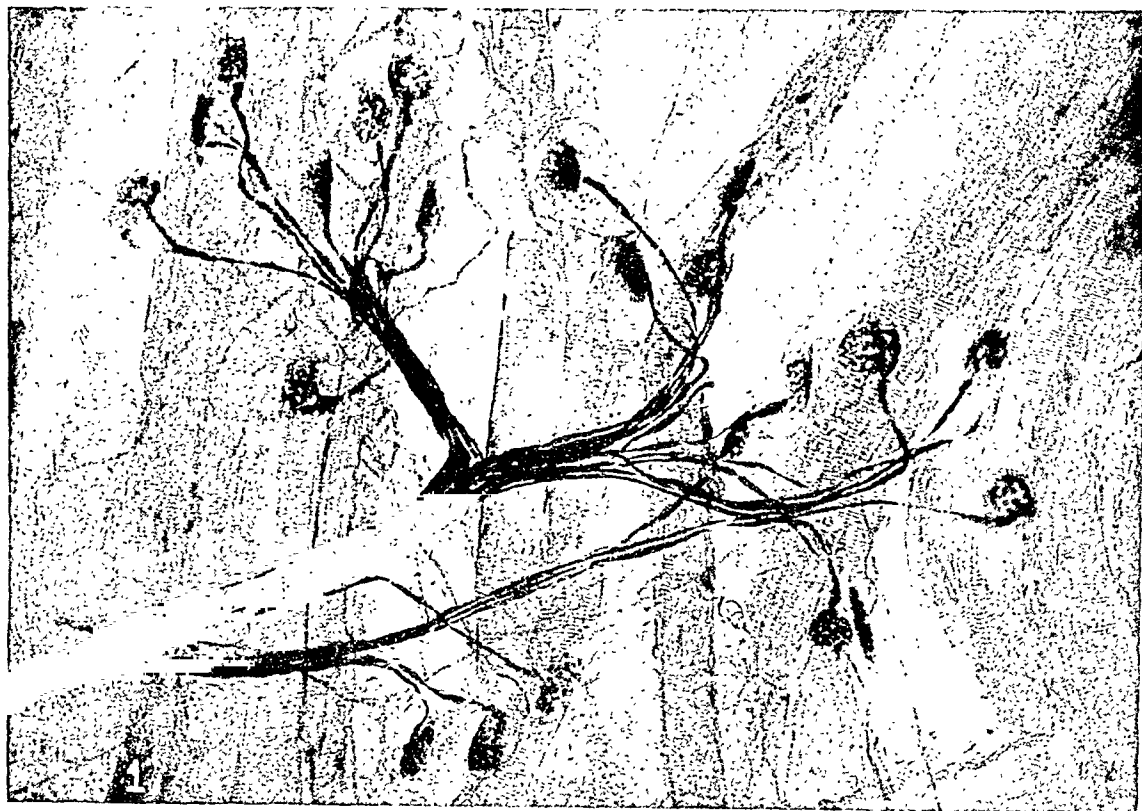
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[Illustrations follow]

DESCRIPTION OF PLATES

PLATE 172

FIGS. 1 and 2. The teased normal innervation of the left quadriceps femoris muscle (Fig. 1) in the monkey is contrasted with that in the left quadriceps femoris muscle (Fig. 2) on the first day of paralysis. In the normal (Fig. 1) there is a variation in the size of the motor end-plates and there are present muscle fibers that are darkly and lightly stained with gold. On the first day of paralysis (Fig. 2) some of the motor end-plates, which stain deeply with gold, are uniformly retracted, and there is a loss of the differential types of muscle fibers. There is passive hyperemia of the capillaries of the muscle fibers (Fig. 2).
X 150.

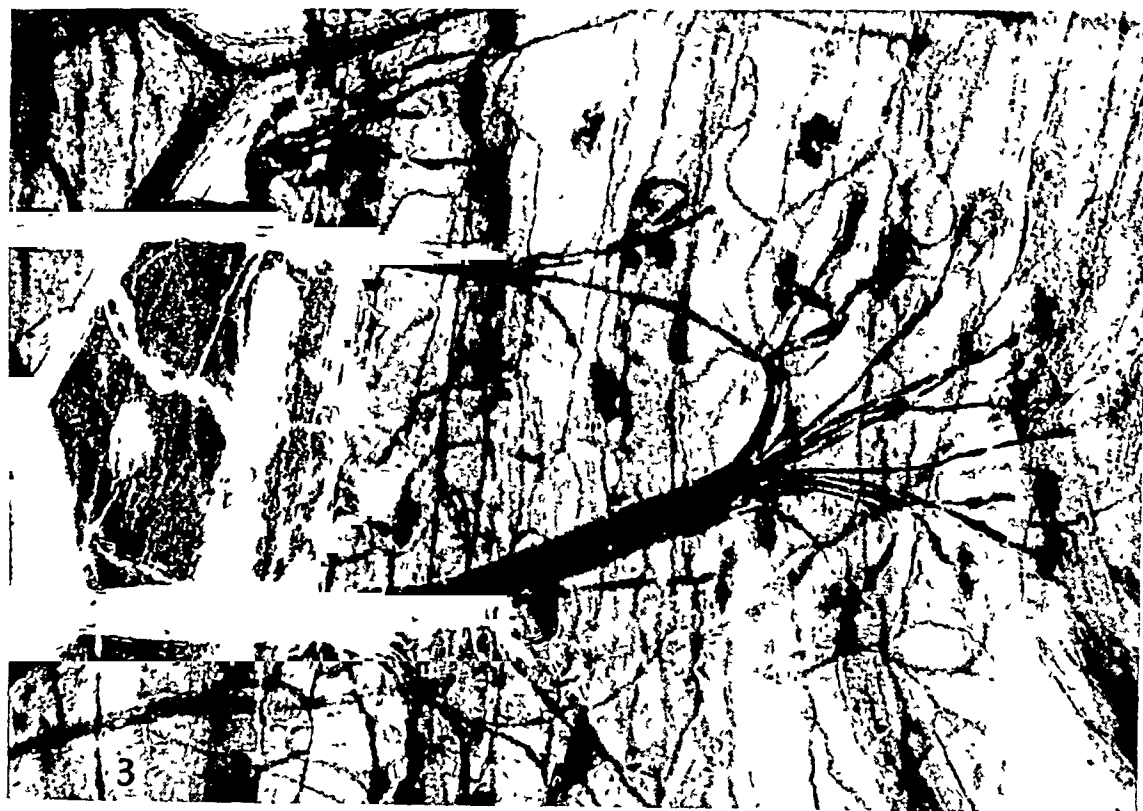


Carey

Effects of Poliomyelitis on Neuromuscular Mechanism

PLATE 173

FIGS. 3 and 4. The teased innervation of the nonparalyzed but weakened gastrocnemius muscle from a monkey in which the upper extremities were paralyzed for 1 day. There is definite enlargement and hyperemia of the intramuscular blood vessels. The motor end-plates are in variable degrees of retraction, and some are in a state of granular fragmentation. The epilemmal axons are beaded and in some places fragmented. $\times 150$.

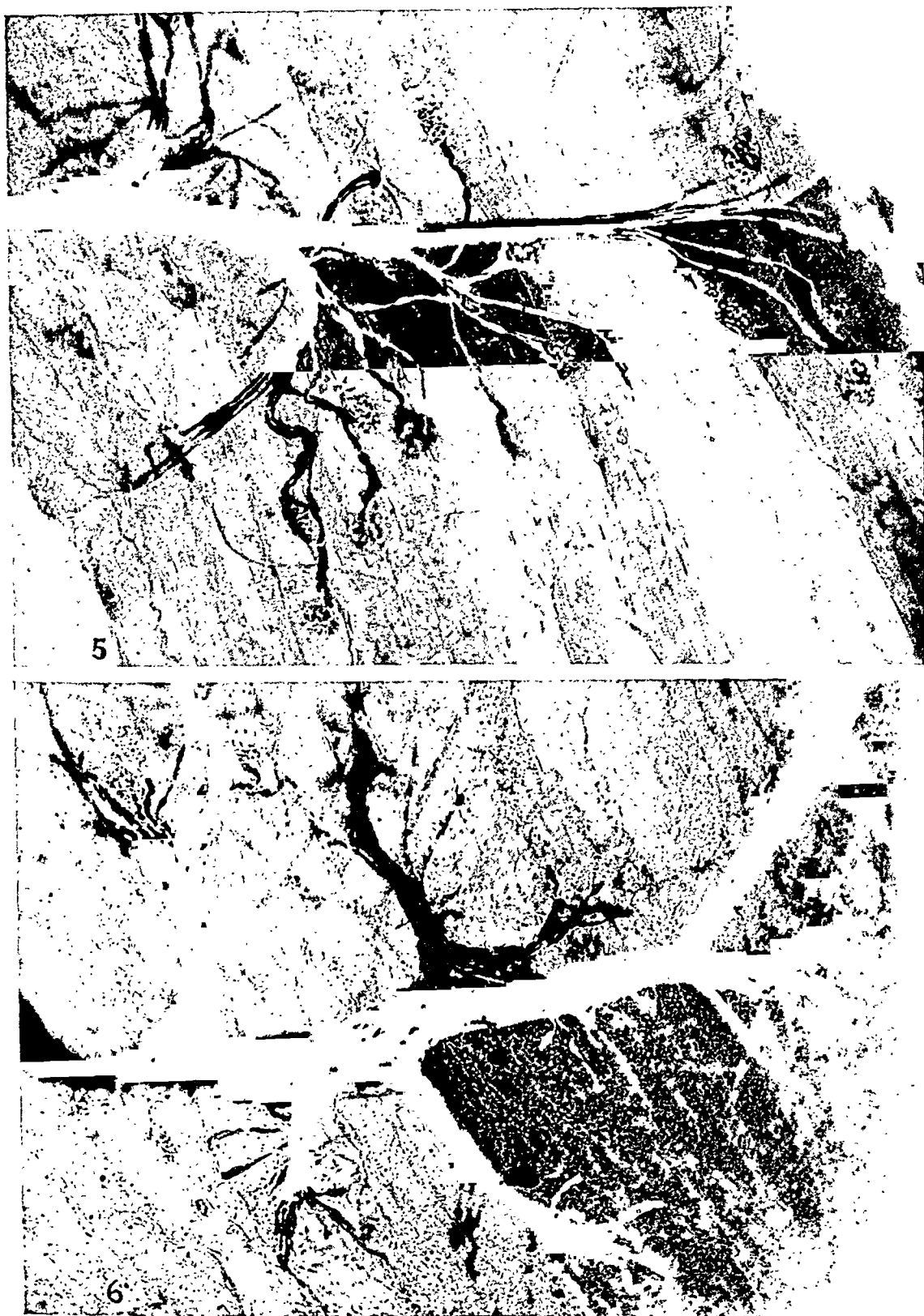


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PLATE 174

FIGS. 5 and 6. The teased innervation of the nonparalyzed but greatly weakened triceps muscle (Fig. 5) in contrast to the paralyzed biceps brachii muscle (Fig. 6) from the same monkey (no. 490, Kramer's series). The hypolemmal axons of the motor end-plates are fragmented into granules which have a stippled pattern and take a deep stain with gold (Fig. 5). The epilemmal axons are irregularly beaded. The motor end-plates have completely disappeared in the biceps brachii muscle (Fig. 6) except in a few locations where a diffuse granulation is found. The epilemmal axons are definitely enlarged, shortened and beaded, and terminate in rounded or ovoid bulbs which are enlarged and are stained deeply with gold. In many places the cross striations of the muscle fiber have disappeared and a diffuse granulation is present. $\times 150$.

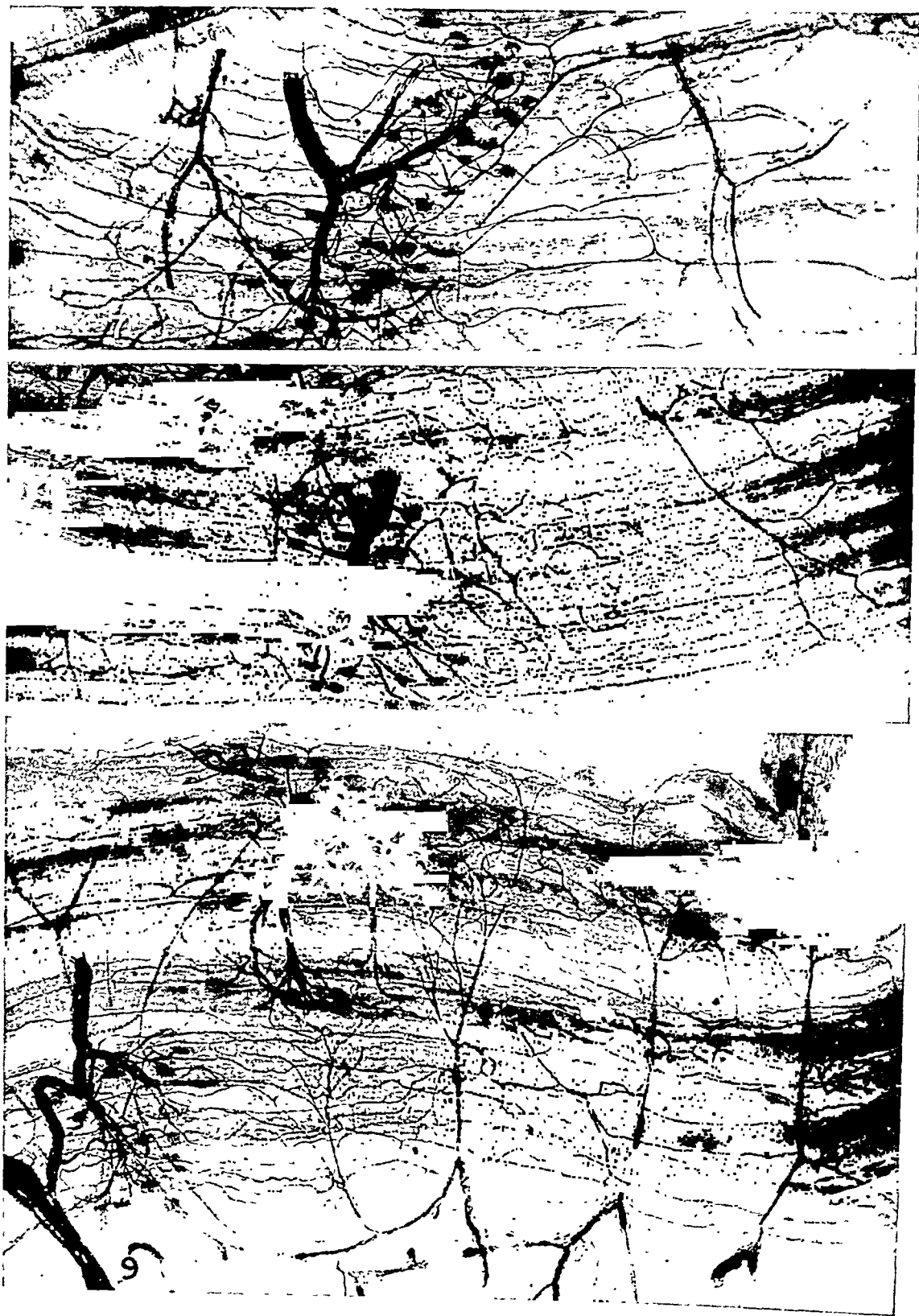


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PLATE 175

FIGS. 7, 8 and 9. The teased motor innervation from the nonparalyzed but weakened biceps femoris muscle (Figs. 7, 8 and 9) 1 day after the onset of the paralysis of both upper extremities. There was muscle weakness associated with a striking passive hyperemia and enlargement of the capillaries and the intramuscular vessels, with beginning perivascular infiltration of leukocytes and a few lymphocytes. There is increased visibility in the nuclei of some muscle fibers (Fig. 8) arranged in longitudinal rows. A majority of the motor endplates show retraction and increased staining capacity. There is beading of the epilemmal axons. The content of the congested blood vessels has increased staining affinity for gold. $\times 80$.



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PLATE 176

FIGS. 10 and 11. Teased innervation of the nonparalyzed but weakened biceps brachii muscle (Fig. 10) of the monkey. There is definite granular degeneration of some muscle fibers and passive hyperemia of the intramuscular capillaries. The epilemmal axons are shortened and beaded, and the hypolemmal axon of the end-plate is retracted into rounded, deep-staining terminals. The motor innervation of the paralyzed triceps muscle (Fig. 11) is from the opposite limb to that illustrated above (Fig. 10). There is a loss of the majority of the motor end-plates and the faint outline of those present is occupied by granules diffusely arranged. The epilemmal axons are retracted, beaded, enlarged, and have intense affinity for gold. $\times 80$.



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Effects of Polomyelitis on Neuromuscular Mechanism

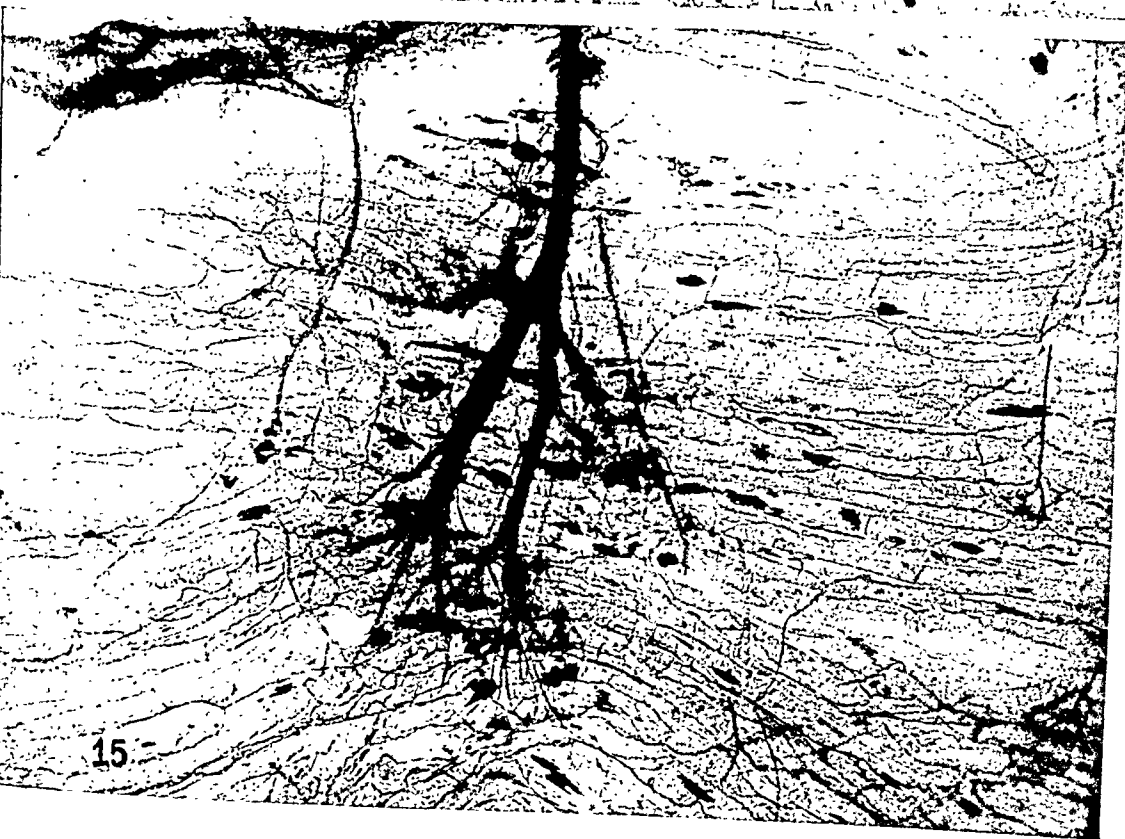
PLATE 177

FIGS. 12 and 13. The motor innervation of the paralyzed right biceps brachii muscle (Fig. 12) of monkey 490, Kramer's series. There is a loss of motor end-plates but there are present multiple masses, both inside and outside of the muscle fiber, that have the same intense affinity for gold as that of the normal axon. It is assumed that these masses were projected from the termination of the axon into the muscle substance. The relationship of these masses to the axonic substance is based upon two factors; namely, (1) similarity of staining capacity and (2) the attenuation of the terminals of the axon simultaneously with the presence of the gold-staining masses in close relationship to the motor innervation. The motor innervation of the left paralyzed biceps brachii muscle (Fig. 13) in the same monkey likewise has these gold-staining inclusion masses in close relationship to the attenuated terminals of the axons. There are endothelial sprouts of new blood vessels in a state of passive hyperemia (Fig. 13).
× 80.



PLATE 178

FIGS. 14 and 15. The teased motor innervation of the paralyzed right gastrocnemius muscle (Fig. 14) of monkey 338, Pearson's series. There is a close relationship of the projected gold-staining masses to the attenuated terminals of the axons. These inclusion masses vary in size from rounded, globoid bodies, 1 to 2 μ in diameter, to masses of these granules that vary from 5 to 105 μ in length. The teased motor innervation of the paralyzed left tibialis anterior muscle (Fig. 15) in the same animal as above (Fig. 14) not only possesses retracted deep-staining motor end-plates but closely related gold-staining inclusion masses which appear simultaneously with the attenuation and, in some instances, with complete depletion of the gold-staining substance of the axons. $\times 80$.



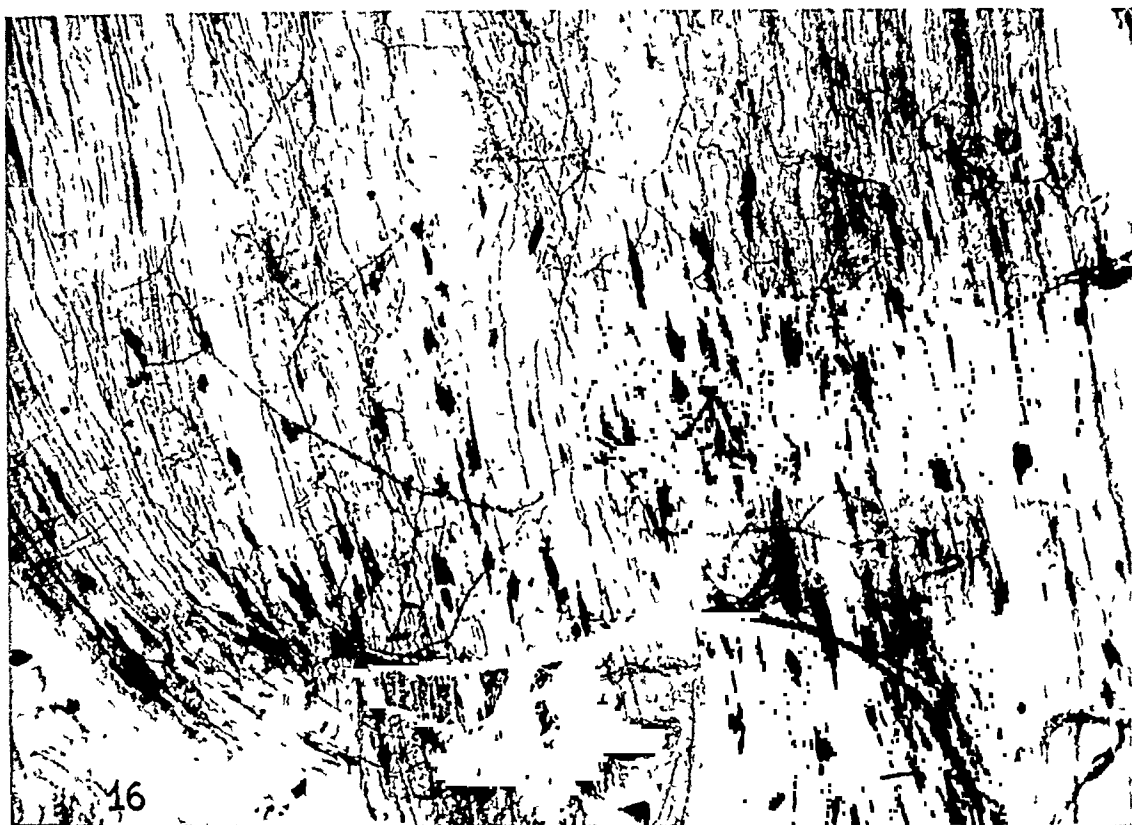
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Effects of Poliomyelitis on Neuromuscular Mechanism

PLATE 179

FIG. 16. The teased motor innervation of the right sternocleidomastoid muscle of monkey 53, Marquette series, had projected gold-staining masses which varied from 5 to 105 μ in length and which were related to the degenerating innervation. The absence of the motor end-plates concomitant with the appearance of the gold-staining projection masses in the muscle fiber is clearly evident. $\times 80$.

FIG. 17. The teased fibers of the weakened right trapezius muscle of monkey 53 had enlarged and congested intramuscular blood vessels. There is evidence of a beginning perivascular infiltration of polymorphonuclear leukocytes and some lymphocytes. Passive hyperemia with enlargement of the blood vessels is one of the earliest signs of pathologic change in the involved muscle. $\times 150$.

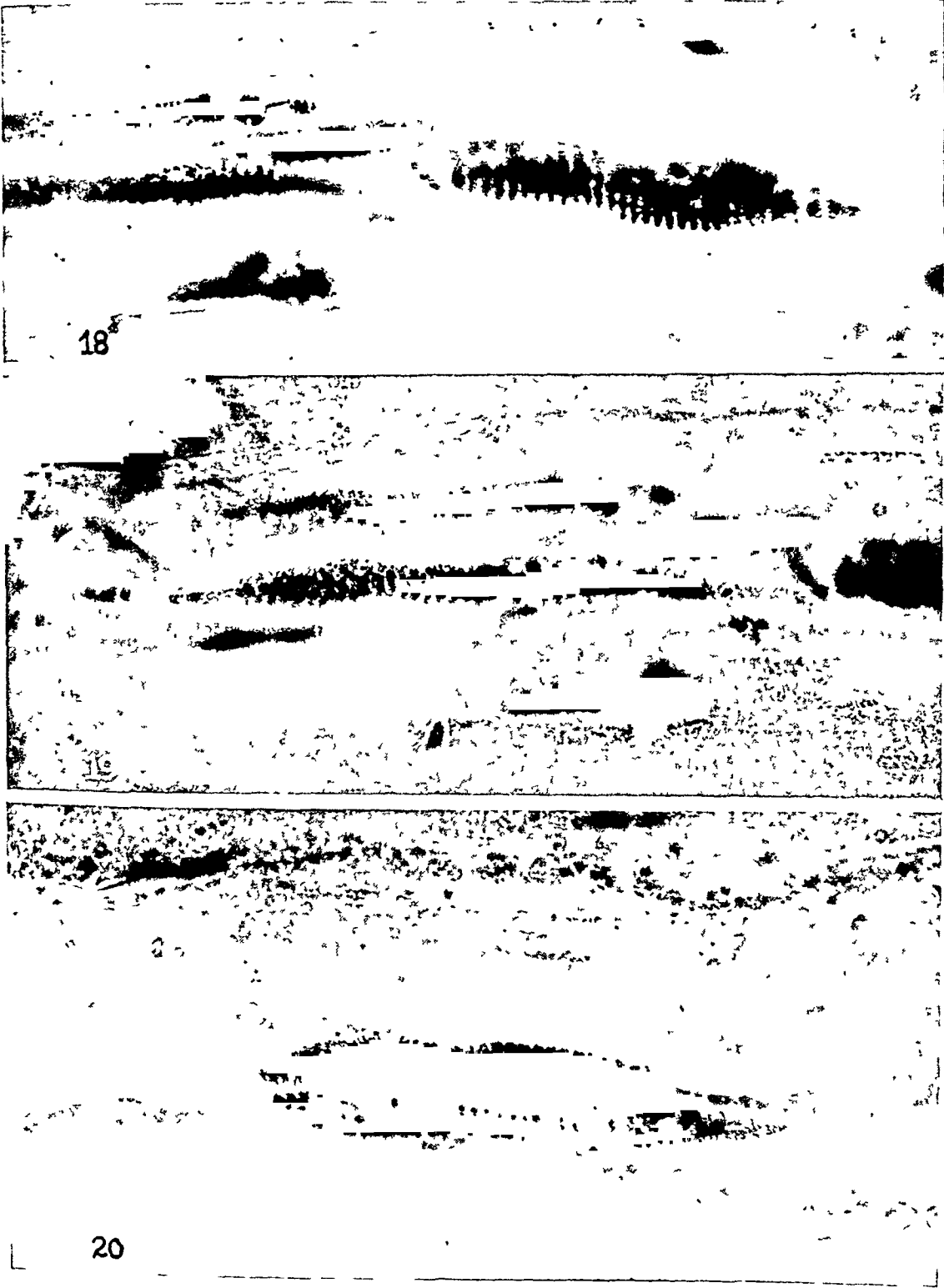


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PLATE 180

FIG. 18, 19 and 20. Elongated projection masses of axonic substance in the paralyzed gastrocnemius muscle (Figs. 16, 17 and 18). These projection masses have a greater affinity for gold than the dark cross striations of the muscle fiber. These masses are composed of rounded bodies 1 to 4 μ in diameter, and in some places are arranged in cross striations. In other places the periphery has a festooned border, the convexities of which correspond with the ordinary dark cross striations of the muscle fiber. (Fig. 18). $\times 750$.



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PLATE 181

FIGS. 21 to 26. Elongated projection masses of axonic substance in the paralyzed gastrocnemius muscle 2 days after the onset of paralysis. Some of these projection masses have a deep uniform stain, the border of which is festooned (Fig. 21). In others there is a definite arrangement of the globoid granules into cross striations. Some of these globoid granules arranged in cross striations are surrounded by a light circular border (Fig. 26). In some places these granules are aligned to correspond with the normal cross striations of the muscle. In other locations they have a periodicity of their own which does not correspond to the immediately related cross striations in the muscle fiber (Fig. 26). These axonic projection masses have a more intense affinity for gold than that of the cross striations of the muscle. In some places (Fig. 25) there is a diffuse arrangement of the projected axonic granules in relationship to others which are definitely cross striated. $\times 750$.

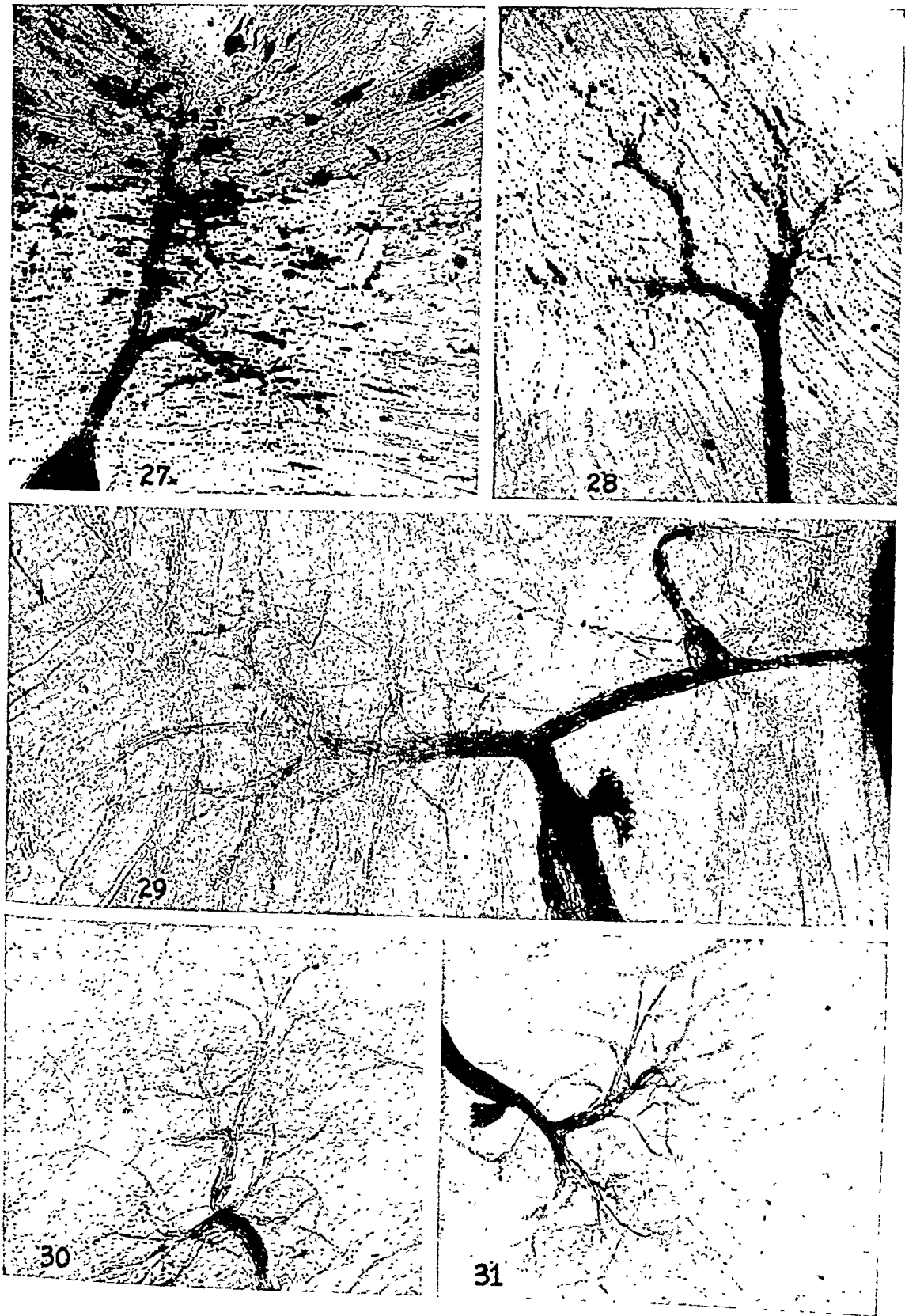


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PLATE 182

FIGS. 27 to 31. Elongated projection masses of axonic substance in the paralyzed biceps brachii muscle. It may be noted that corresponding with the presence of the axonic masses projected into the substance of the muscle fiber there is a decrease of gold-staining material in the axons, 4 days after the onset of paralysis (Figs 27 and 28). There is an absence of gold-staining axonic masses in the paralyzed triceps muscle (Figs. 29, 30 and 31), 4 days after the onset of paralysis, taken from the same limb (Figs. 27 and 28). There is a diminution or complete depletion of the substance in the axonic terminals. This pathologic change appears to progress in a centripetal direction from the original location of the motor end-plates. The terminal epilemmal axons in some places (Figs. 29, 30 and 31) have merely a faint ghost-like outline with no affinity for gold, or a greatly decreased staining capacity for gold. $\times 80$.

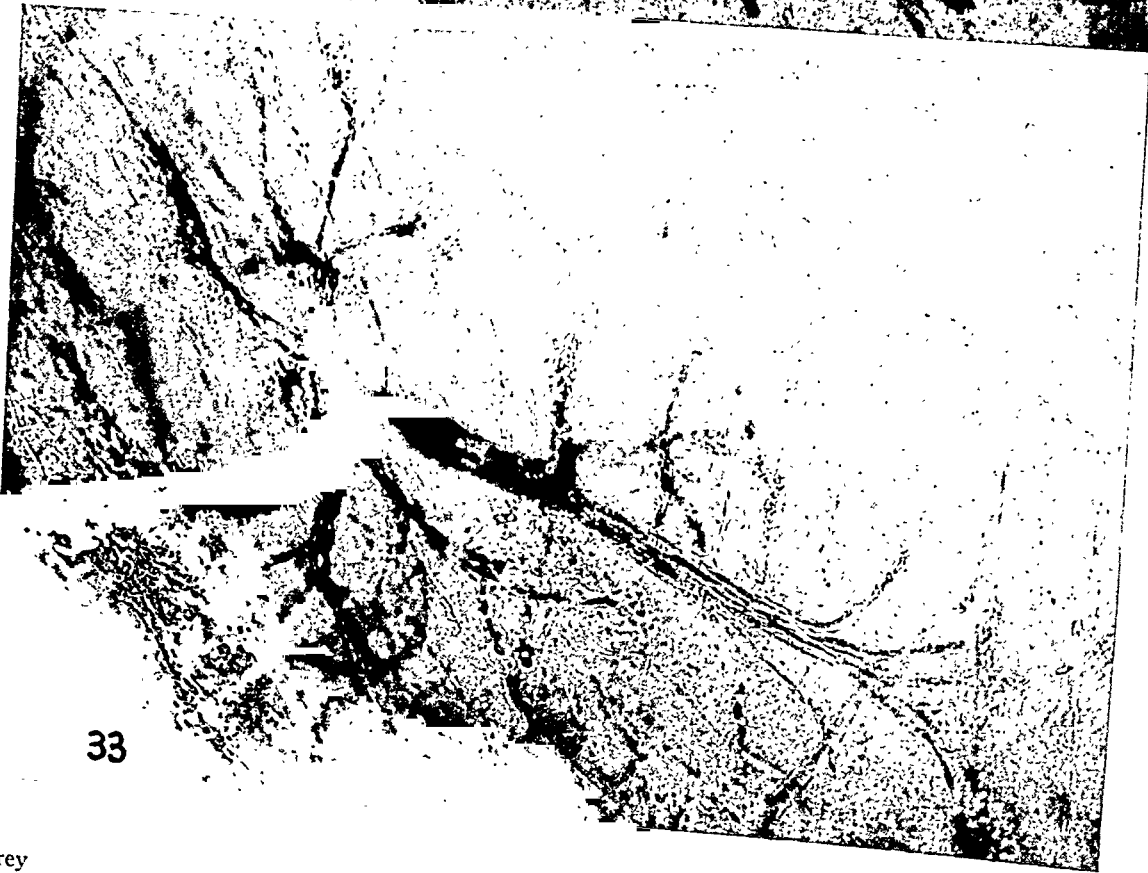
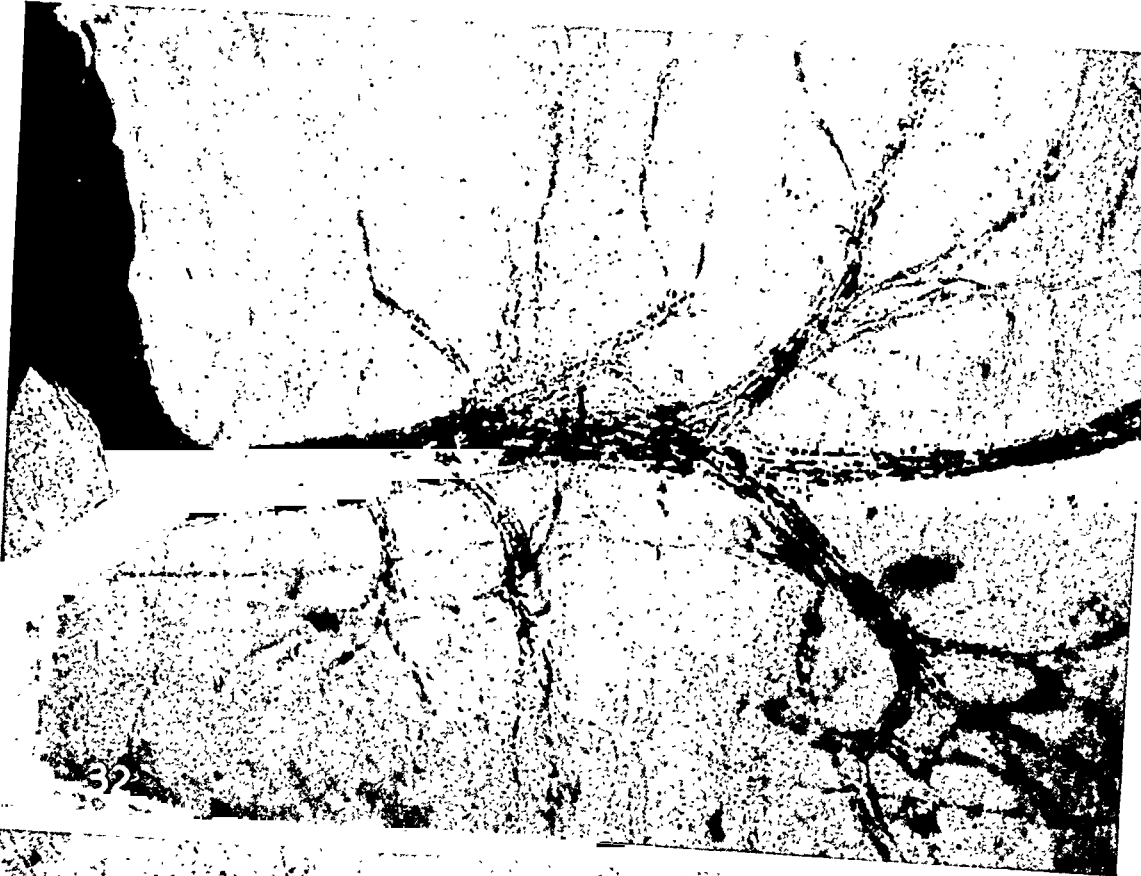


Carey

Effects of Poliomyelitis on Neuromuscular Mechanism

PLATE 183

FIGS. 32 and 33. There is a decrease, or a complete exhaustion, of the gold-staining substance in the terminal axons of the motor innervation of the paralyzed triceps muscle, 4 days after the onset of paralysis. This pathologic change appears to progress in a centripetal direction from the original location of the motor end-plates. The terminal epilemmal axons in some places (Figs. 32 and 33) have merely a faint ghost-like outline with no affinity for gold or a greatly decreased staining capacity for gold. Corresponding to the complete depletion of the substance in the terminal axons there is an eventual disappearance of the axonic inclusion masses that were originally projected into the substance of the muscle fiber. In some places, the cross striations of the muscle fibers are replaced by a disorganized mass of granules and in others by a more hyaline appearance comparable to Zenker's waxy degeneration. $\times 250$.



Effects of Poliomyelitis on Neuromuscular Mechanism

CONGENITAL GASTRO-ENTERIC CYSTS OF THE MEDIASTINUM

A REVIEW AND REPORT OF A CASE *

HARRY G. OLKEN, M.D.

(From the Department of Pathology, Tufts College Medical School, Boston, Mass.)

Tumors of the mediastinum, as a group, are not common, and of these only a minor percentage are cystic.¹ Cysts of the mediastinum are usually congenital and represent for the most part dermoid or teratoid tumors. Other cysts have been described in association with the various structures of the mediastinum. The simplest of these are represented by the pericardial celomic cysts² and the cystic lymphangiomas.³ The so-called bronchiogenic cysts, although somewhat more common, are also more complex.⁴ The latter are lined with ciliated cylindrical epithelium, contain mucous glands, muscle and cartilage, and are referred to misplaced portions of the respiratory tract. Still another group of cysts are lined by mucous membrane resembling some portion of the intestinal tract and are classed as enteric or gastric cysts.⁵

The following case falls into this latter category of gastro-enteric cysts of the mediastinum, of which fewer than 20 have hitherto been reported in the literature.

REPORT OF CASE

(Tufts Medical School, Pathology no. A-41-2.) A full-term, male, stillborn fetus weighing 7 lbs. was delivered at the Evangeline Booth Maternity Hospital. The mother was a healthy white primipara. The child showed hydrocephalus and spina bifida on external examination. Autopsy revealed additional findings involving not only the central nervous system but also the thoracic cavity.

The head was enlarged and the suture lines widely separated. Over the lower thoracic and upper lumbar area of the back there was a large cutaneous defect (4.0 by 2.5 cm.), associated with an underlying defect in the spinal column, in which the arches had failed to close. From the cervical region to the sacrum there was only one completely fused arch—the first thoracic. There was, furthermore, herniation through the foramen magnum of the elongated cerebellum, which extended down the vertebral canal, overlying the spinal cord. The tonsils of the cerebellum lay at the level of the first thoracic vertebra. At the mid-thoracic region the spinal cord split into two flattened ribbons which were incorporated in a meningocele. The cranial bones showed numerous, irregular fenestrations. The dura was completely absent within the cranial cavity. The gyri of both hemispheres were small.

* Received for publication, December 24, 1943.

Exposure of the thoracic cavity showed a small, bilobed, right lung, which was compressed by a large cystic mass extending from the posterior mediastinum and occupying the greater portion of the right thorax. The mass lay behind the pleura, and showed no communication with the trachea, esophagus, or any other mediastinal structure (Fig. 1). The heart and the left lung were pushed to the left. The cyst extended from the right apex to the diaphragm and measured 8.0 cm. in greatest length by 4.0 cm. in greatest diameter. It contained thick, clear, mucoid fluid. Its wall varied in thickness from 0.2 to 0.4 cm., and its inner surface was smooth. Sections were removed for histologic examination. The organs of the abdomen showed no anomalies.

Anatomic Diagnoses. (Gastrogenic) cyst of the posterior mediastinum.

Spina bifida with diplomyelia and myelomeningocele; Arnold-Chiari malformation⁶ of the cerebellum (herniation of the cerebellum into the spinal canal); microgyria; congenital absence of the dura, including tentorium, falx, and dural sinuses; congenital fenestration of the cranial bones (craniolacunia). Hydrocephalus. Bilobed right lung.

Microscopic Examination of the Wall of the Mediastinal Cyst

The wall of the mediastinal cyst varied in thickness and in structure. In areas it was thin and composed of a few muscle fibers and loose connective tissue. In other areas distinct muscle layers (circular, transverse and oblique) were noted. Varying amounts of lymphoid tissue were seen in different areas of the wall. The cyst was lined with mucosa, although in places it was denuded. The mucosa varied from a simple layer of cuboidal, nonciliated epithelium, a single cell in thickness, to a well differentiated gastric lining in which mucus-secreting glands and acid-secreting cells were identified (Figs. 2, 3 and 4).

REVIEW OF THE LITERATURE

An intensive search revealed 18 well defined cases of gastro-enteric cysts of the mediastinum. In the following table these cases are summarized in brief.

Although so small a series does not lend itself to statistical analysis, many interesting features appear to be common to the group. Somewhat more common in males than in females, these cysts, for the most part, occupy the right hemithorax, although occasionally they are found on the left side or in a median position. Most striking is the early age at which symptoms are produced. Seventy-five per cent of the cases were discovered within the first year of life and in only two instances^{19, 22} were the children as old as 3 years. This is in sharp

Summary of Reported Cases

No.	Author (year)	Sex and age	Description of mediastinal cyst	Other anatomic findings, and remarks
1	Hennig ⁷ (1880)	F Newborn	Extended into left pleural cavity, from 3rd to 5th vertebra; size of plum; lined with simple cylindrical epithelium	Intramesenteric cyst lined with similar epithelium
2	Roth ⁸ (1881)	M Newborn	Extended into right pleural cavity; lined with "typical intestinal mucosa"	Two enteric cysts of abdomen lined with similar epithelium, plus a diverticulum of ileum extending between the layers of mesentery
3	Staehelein-Burckhardt ⁹ (1909)	F 9 mos.	At lower end of esophagus on right side; size of hen's egg; wall showed structure of both stomach and esophagus plus areas of ciliated epithelium	Spina bifida and uvula bifida; diverticulum of urinary bladder
4	Schmincke ¹⁰ (1920)	M 15 da.	Extended into right thoracic cavity; size: 4.5 by 4.3 by 4.0 cm.; lined with small intestinal mucosa	Intramesenteric enteric cyst; congenital scoliosis; extra lobe of right lung
5	Mixter and Clifford ¹¹ (1929)	M 22 mos.	Filled two-thirds of right thorax, extending from apex to diaphragm; 6.6 cm. in average diameter; lined with gastric mucosa	No other anomalies noted; cyst removed surgically, and child recovered
6	Mixter and Clifford ¹¹ (1929)	M 7 wks.	Bilocular cyst lay for the most part in the right thorax; 5.0 cm. in greatest diameter; lined with typical gastric mucosa	No other anomalies noted; removal attempted, but child died
7	Smith ¹² (1930)	M 13 mos.	Posterior mediastinal cyst occupied portion of right thorax; size: 12.5 by 3.8 by 3.8 cm.; lined in part by gastric mucosa and in part by ciliated and stratified epithelium	No other anomalies noted at autopsy
8	Fischer ¹³ (1930)	F 6 mos.	Paravertebral cyst, extended from clavicle to diaphragm behind right lung; size: 8.0 by 4.0 cm.; lining "characteristic of intestines, with areas suggestive of pyloric mucosa"	Scoliosis; accessory spleen
9	Entz and Orosz ¹⁴ (1930)	M 11 mos.	Extended into right thorax; size: 10 by 7 by 2.0 cm.; lined with mucosa characteristic of fundal portion of stomach	Scoliosis; mental retardation (clinical); cyst incised and drained; died in 18 days
10	Poncher and Milles ¹⁵ (1933)	M 29 mo.	Two cysts of posterior mediastinum extended into right thorax; larger measured 12 by 10 cm.; smaller, 6 by 3 cm.; lined with "typical gastric mucosa"	Intramesenteric diverticulum arising from ileum, containing gastric mucosa with peptic ulcer; died during attempted removal of larger cyst

No.	Author (year)	Sex and age	Description of mediastinal cyst	Other anatomic findings, and remarks
11	Stoeckel ¹⁶ (1935)	F Pre-mature, newborn	Size: 5 by 3.5 cm.; straddled the vertebral column at level of 2nd to 6th ribs; constricted in center to form 2 connected cysts; lined with columnar nonciliated epithelium	Abnormal vessel arose from arch of aorta
12	Black and Benjamin ¹⁷ (1936)	M 4½ mos.	Retropleural cyst (14.0 by 6.5 cm.) extended into left pleural cavity from 3rd to 12th vertebra; lined with elongated and flattened mucosal cells	Diverticulum of jejunum with a peptic ulcer which had ruptured and produced peritonitis
13	Brass ¹⁸ (1936)	F Pre-mature	Kidney-shaped cyst extended into right pleural cavity (7.1 by 3.5 cm.); supplied by intercostal arteries and vagus nerve; lined with "typical small intestinal mucosa"	Uvula bifida
14	Böss ¹⁹ (1937)	M 3¾ yrs.	Cyst extended into right thorax; size of hen's egg; lined with mucosa resembling fundal portion of stomach; peptic ulcer of cyst had ruptured in lower lobe of right lung	No other anomalies; died of hemorrhage during second stage of attempted removal
15	Guillery ²⁰ (1937)	Sex ? 3 mos.	Cyst of posterior mediastinum lay on the vertebral bodies from 3rd to 7th thoracic vertebra; size: 5 by 2.5 cm.; second smaller cyst (1.5 by 0.8 cm.) behind 5th thoracic vertebra within spinal canal; both lined with cylindrical epithelium	Distortion of 5th thoracic vertebra
16	Seydl ²¹ (1938)	F 3½ mos.	In posterior mediastinum, between esophagus and lower lobe of right lung; size: 3.5 by 1.7 by 1.7 cm.; lined with gastric mucosa and contained a peptic ulcer which had perforated into lung and had eroded a large vessel, causing fatal hemorrhage	Left-sided scoliosis; obliterative pleuritis
17	Nicholls ²² (1940)	F 3 yrs.	Right-sided retropleural cyst filled most of right thorax; lined with gastric mucosa	Dorsal scoliosis; cyst incised at age of 3, following which draining sinus developed; completely excised at age of 8, with good healing
18	Carlson ²³ (1943)	M 4 mos.	Cyst of posterior mediastinum lined with gastric mucosa	No other anomalies; completely and successfully removed
19	Author	M Newborn	Occupied greater portion of right thorax; size: 8 by 4 by 4 cm.; extended from apex to diaphragm; lined with gastric mucosa with areas of simple cuboidal cylindrical epithelium	Spina bifida; Arnold-Chiari malformation of cerebellum; absence of dura; craniolacunias; hydrocephalus; bilobed right lung

contrast to the mediastinal dermoid tumors which produce practically no symptoms over a period of years while the cyst is undergoing progressive growth and expansion. Of 139 thoracic dermoids and teratomata collected by Kerr and Warfield²⁴ in 1928, including their own case, only 11 occurred in the first decade of life.

It is a well known axiom in pathology that congenital anomalies are very frequently multiple. This series of cases is no exception, for in almost all instances the thoracic cyst was associated with one or more other anomalies of development. Of the 19 cases analyzed, only 3 failed to show some other developmental anomaly in addition to the mediastinal cyst. The intestinal tract and skeletal system were most frequently affected. In 5 of the 19 cases, single or multiple intra-abdominal enteric cysts, or intestinal diverticula, or both, were found with the gastric or enteric cyst of the thorax. In 8 cases the vertebral column was involved. Usually this involvement was limited to a simple scoliosis, but in some instances the vertebral bodies themselves were misshapen and in 2 instances a severe spina bifida was present.

The majority of the mediastinal cysts were lined, at least partially, by histologically identifiable gastric mucosa (12 of the 19). The mucosal linings of the others were more suggestive of small intestinal epithelium. Böss¹⁹ and Seydl²¹ reported active peptic ulcers within the mediastinal cysts and in both instances the ulcers had perforated into neighboring structures. Poncher and Milles¹⁵ and Black and Benjamin¹⁷ also found active peptic ulcers, but in their cases the ulcerations were within the intestinal diverticula which were associated with the mediastinal cysts. This high incidence of peptic ulceration in ectopic gastric mucosa offers an interesting problem for the physiologist and clinician.

The knowledge of these mediastinal anomalies and the improvement in the technics of thoracic surgery have permitted some hope of successful therapy. In at least 7 instances surgical removal of the mediastinal cyst was attempted, and in 3 instances the operation was successful, and recovery complete.

DISCUSSION

Intraperitoneal enteric cysts constitute a rather well defined group of tumors.²⁵ Appearing as single or multiple cysts of varying size, they resemble in structure the intestines, containing smooth muscle, mucosa, crypts, lymphoid tissue, and a lining of cylindrical, cuboidal, or stratified epithelium. They are usually associated with the small bowel or its mesentery, being situated either at the navel or at the lower end of the ileum. Some, however, have appeared in the cecum²⁶ or even as

low down as the rectum.²⁷ These enteric cysts have usually been accepted as originating from Meckel's diverticulum, the omphalomesenteric duct, or from definitely misplaced portions of the intestines.⁵

The appearance of such cysts above the diaphragm has complicated, somewhat, the problem of genesis. Many of the mediastinal cysts which have been described were lined with intestinal epithelium and resembled in all detail the intra-abdominal enteric cysts. An even greater proportion of these mediastinal cysts were lined with gastric mucosa. There is still another group of mediastinal cysts arising from the digestive tract which complicate the picture even further, and should be included in this discussion. These are the esophageal cysts which, because of their position and gross appearance, may be confused with the gastric or enteric cysts of the mediastinum.

Although there can be no doubt that all of these mediastinal cysts are closely related embryologically, the esophageal cysts seem to form a rather distinct group. Several have been described.²⁸⁻³⁶ Almost invariably found in adults, they are situated in the lower half of the esophagus, usually between the muscle layers of the esophageal wall. The epithelium is composed of ciliated cuboidal cells with occasional foci of flattened epithelial cells. Histologically these cysts resemble most closely the group described as of bronchiogenic origin,⁴ except that the esophageal cysts contain no cartilage.

A discussion of the origin of gastric and enteric mediastinal cysts cannot be dissociated from a consideration of esophageal and bronchiogenic cysts. There is much histologic overlapping. Smith¹² and Staehelin-Burckhardt,⁹ for example, reported mediastinal cysts which were lined in part with gastric and in part with ciliated epithelium. Cilia are not restricted to respiratory epithelium. In many regions of the body there occur small or large cysts with ciliated epithelium. In the case of the esophageal cysts, the epithelium is undoubtedly a remnant of the embryonic esophageal epithelium which is ciliated.³⁷ Also the esophagus and trachea arise in close union. In the 4 mm. pig the lung buds appear attached to the ventral border of the esophagus. The trachea becomes separated from the esophagus by the downward growth of the lung buds and the upward extension of the notch between the lung buds and the esophagus.³⁸ Mixter and Clifford¹¹ believed that this phenomenon might also account for the appearance within the mediastinum of gastric cysts. They pointed out that:

"... The fusion of the lateral walls to form the tracheo-oesophageal septum begins from below. It would seem that at this embryonic stage, the pinching off of an outbud or diverticulum of foregut containing entoderm and mesoderm, and destined to become a portion of the stomach might well occur. This could be carried along by the downward growing lung bud and lodge in the mediastinum or on the surface of the lung."

There is probably more than one explanation for gastro-enteric mediastinal cysts, however. Black and Benjamin,¹⁷ among others, believed that they represent an intrathoracic vestige of the ductus omphalomesentericus (vitelline duct). They repeat the observation made long ago by Fitz³⁹ that the persistence of the vitelline duct accounts for many cases of intestinal duplication and cyst formation. It is generally accepted that many intra-abdominal variations in intestinal development are due to persistence and growth of vitelline duct remnants. Since the thoracic and abdominal cavities are not differentiated at that period of fetal life when the vitelline duct is present, it is conceivable that this duct might also account for developmental defects within the thorax. In fact, in the case recorded by Black and Benjamin the intrathoracic cyst was associated with a reduplicated intramesenteric intestinal pouch, a defect long attributed to vitelline duct persistence.

Several of the gastric and enteric cysts of the mediastinum were associated with other intra-abdominal enteric cysts or diverticula, some of which were found within the leaves of the mesentery. Poncher and Milles¹⁵ believed that it is difficult to correlate the wide variety of positions of these enterogenous cysts or diverticula with vitelline duct rests. They claimed that:

"... at the time of obliteration of the vitelline duct in the 7 mm. embryo the dorsal mesentery and its vessels are already well developed. In the case of the intramesenteric cysts and diverticula it is necessary to postulate that the duct remnants not only insert themselves between the well formed leaves of the dorsal mesentery, but also between its vessels, deriving an entirely new blood supply from them."

Poncher and Milles were, therefore, more prone to seek another source for these widely separated anomalies, and they found their explanation in the epithelial nodules of Lewis and Thyng.⁴⁰ These "epithelial nodules" are definitely misplaced portions of the intestines which can be traced to small diverticula of the gut occurring in fetal life. Such diverticula are apparently not uncommon in human and animal embryos, and occur at a time when their persistence would place them between the leaves of the mesentery or within the thoracic cavity.

In summary, then, we find at least three possible explanations for these enteric and gastric cysts. They have been ascribed to the pinching off of a bud or diverticulum of the embryonic foregut; to an intrathoracic remnant of the omphalomesenteric duct; and to an embryonic diverticulum or epithelial remnant capable of producing intestinal or gastric mucosa ("epithelial nodules" of Lewis and Thyng⁴⁰). Probably all three mechanisms play some part in their genesis.

SUMMARY

Congenital gastric and enteric cysts of the mediastinum are rare. A case of a gastric mediastinal cyst is reported and the literature, including 18 previously recorded cases, is reviewed. The origin of such cysts and their relationship to bronchiogenic and ciliated esophageal cysts is discussed.

A study of these 19 cases has failed to reveal an exact reduplication of dysontogenetic patterns, yet it should be pointed out that the common association of mediastinal cysts, mesenteric cysts or diverticula, and deformities of the skeletal system is an interesting finding that is worthy of academic and practical consideration.

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DESCRIPTION OF PLATES

PLATE 184

FIG. 1. Photograph showing the size of the cyst and its relationship to the right pleural cavity. The esophagus is held aside.



1

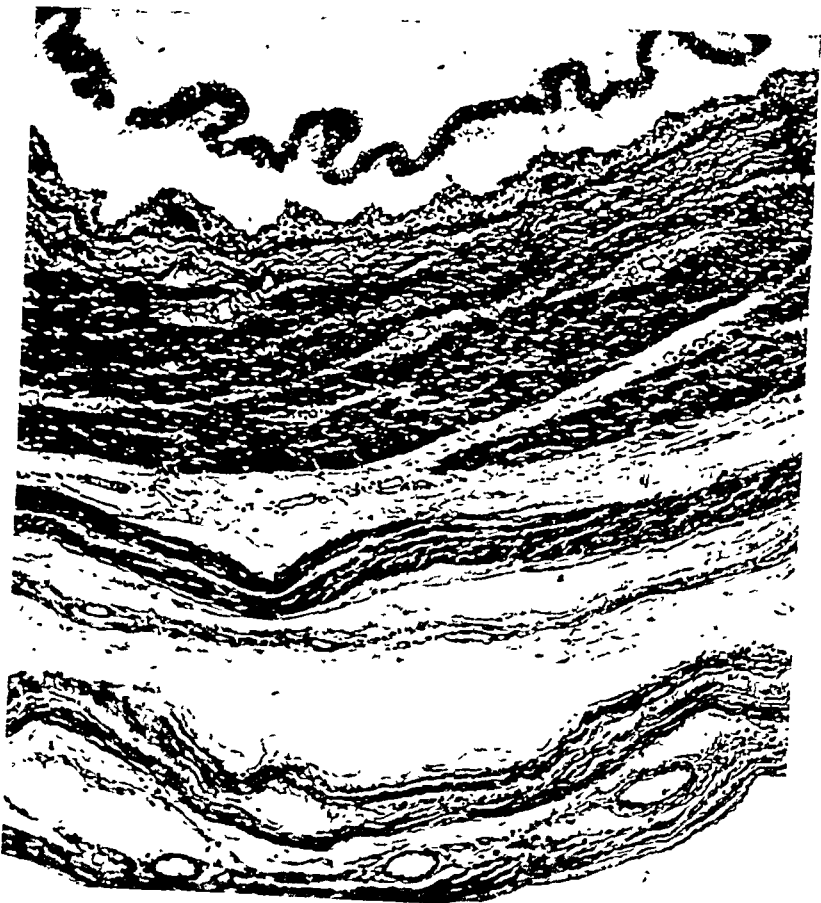
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Gastro-enteric Cysts of the Mediastinum

PLATE 185

- FIG. 2. A section of the cyst wall showing a simple epithelial lining, one cell in thickness. The mucus-secreting cells are not ciliated. Hematoxylin and eosin stain. $\times 86$.
- FIG. 3. A second section of the cyst wall showing a more highly developed mucosa. The arrangement of the muscle layers is well shown. Hematoxylin and eosin stain. $\times 8$.
- FIG. 4. A detailed view of the mucosa shown in Figure 3. The mucus-secreting epithelium is supported by a loose glandular layer containing acid cells. Hematoxylin and eosin stain. $\times 160$.

2



3



4



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Gastro-enteric Cysts of the Mediastinum

DIFFUSE GLOMERULONEPHRITIS FOLLOWING REVACCINATION FOR SMALLPOX*

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In the winter of 1942-43, following an outbreak of smallpox in southeastern Pennsylvania, many thousands of people were vaccinated. While most of these suffered no ill effects, there were occasional patients who did develop untoward sequelae. Locally there were at least two cases of generalized vaccinia and one of fatal diffuse glomerulonephritis. The latter is of particular interest because a thorough search of the medical literature, as far back as 1900, discloses no report of such a fatality. There is only one record, that of Saldún¹ in 1932, who described a boy, 8 years old, who developed unequivocal signs and symptoms of acute diffuse glomerulonephritis 14 days after vaccination, and who later made an uneventful recovery. The following is therefore the first case to be reported with autopsy findings.

REPORT OF CASE

A white laborer, 64 years old, was vaccinated on January 11, 1943, together with many other fellow employees. On January 15th he developed a generalized "macular" rash. He was first seen by the referring physician on January 18th because of pain in the lower back. By this time the original eruption had almost completely resolved but there was a marked reaction at the site of vaccination and there were now present scattered pustules in the skin of the same arm. The blood pressure was elevated. Urinalysis was first performed on February 4th, although several days previously the patient had noted that the urine was grossly discolored. It showed a specific gravity of 1006, 4 plus albumin, coarsely granular casts, pus cells and erythrocytes. Bed rest did not alleviate the pain in the back, which radiated anteriorly and to the groin. The referring physician stated categorically that prior to the vaccination, or during the present illness, the patient did not have an upper respiratory infection of any kind. He had been vaccinated only once before and that was 30 years previously.

He was admitted to Jefferson Hospital on February 9th, 29 days after vaccination, in a semicomatose state. Physical examination disclosed a dry, red and fissured tongue; a "uremic" odor to the breath; a distended and tympanitic abdomen and slight pretibial pitting edema. The throat was normal. The bladder was catheterized but yielded only ½ oz. of turbid urine which on examination showed the same constituents as on February 4th. On February 13th the posterior and lateral walls of the pharynx became edematous and the right tonsil was somewhat congested. While the pharyngeal edema gradually subsided until on February 16th it was almost completely resolved, the pretibial edema became increasingly severe. By February 17th the patient was totally irrational and stuporous and he died 37 days after the vaccination.

During his brief stay in the hospital the temperature ranged from 99° to 101° F.; the pulse from 80 to 110 per minute; the respirations from 20 to 36 per minute; and the blood pressure from 160/80 to 200/90 mm. of Hg. The urine repeatedly showed albumin, casts, pus cells and erythrocytes. The urinary output gradually

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decreased from 1580 to 200 cc. per 24 hours while the corresponding intake of fluids varied from 4000 to 1520 cc. per 24 hours. The blood showed anemia and a leukocytosis of 20,000. The nonprotein nitrogen rose from 55 mg. per 100 cc. of blood on admission to 117 mg. per 100 cc. 2 days before death. Two days after admission the total blood proteins were 4.4 gm. per 100 cc., while the albumin was 2.7 gm. per 100 cc. and the globulin was 1.7 gm. per 100 cc. On February 14th a culture from the throat disclosed *Streptococcus viridans*, *Streptococcus anhaemolyticus* and *Neisseria catarrhalis*.

Gross Examination

Necropsy was performed 3½ hours after death. The skin was normal.

The left kidney weighed 295 gm. and measured 12.5 by 8 by 6 cm.; the right weighed 275 gm. and measured 12 by 7 by 5.5 cm. Both were of normal shape and showed no evidence of previous disease. They were firm. The capsules stripped easily leaving smooth, moist, glistening, reddish brown surfaces, scattered throughout which were numerous bright red petechiae. Cut surfaces showed sharp edges and broad cortices and medullas (Fig. 1). They were also reddish brown and disclosed numerous petechiae. The corticomedullary demarcations were obscured. The vessels were prominent but not sclerotic. The peripelvic fat tissue was not increased. There was no dilatation of the calices, pelves, or ureters, but all of the mucosal surfaces to within 6 cm. of the entrance of the ureters into the bladder were intensely hemorrhagic. The mucosa of the left ureter, particularly in the lower part of the hemorrhagic portion, showed in addition many small vesicles which measured as much as 2 mm. in diameter. The walls of the calices, pelves and ureters were thick and indurated.

The urinary bladder was large but empty and collapsed. Its mucosa was intensely hemorrhagic throughout except for the superficial portions of the rugae which were black. The entire urethra, the prostate, seminal vesicles, epididymides and testes were normal.

The heart weighed 590 gm. It showed considerable hypertrophy of the left ventricle and grossly smooth pericardial surfaces. The posterior and inferior pharynx, the larynx, trachea and bronchi showed no inflammation. There was pulmonary congestion and edema but no pneumonia. The spleen weighed 320 gm. The rest of the thoracic and abdominal organs and the spinal cord were grossly normal. Permission to examine the head was not granted.

Microscopic Examination

Microscopic sections of the kidneys showed an involvement of every glomerulus by an inflammatory or proliferative process (Figs. 2 and 3). While some of the glomeruli were diffusely infiltrated with polymor-

phonuclear leukocytes, others showed only focal collections of such cells. Every glomerulus showed an increase of both endothelial and epithelial cells. There were many adhesions between the tufts and Bowman's capsules. The epithelium of the latter showed beginning or advanced proliferation frequently forming definite and conspicuous glomerular crescents (Fig. 3). Scattered throughout many of the tufts and crescents there were considerable numbers of erythrocytes. Occasionally there were also small, irregular collections of pink-staining amorphous or fibrinoid material intermixed with nuclear fragments and polymorphonuclear leukocytes. While in most glomeruli Bowman's space was completely obliterated by either the tuft or crescent, or both, occasionally it was still apparent and contained erythrocytes and polymorphonuclear leukocytes.

Many of the tubules were slightly or markedly dilated and showed varying degrees of tortuosity. The lining epithelial cells were usually intact. Some were greatly attenuated, flat and contained within their cytoplasm granular brown material. Others were slightly or greatly swollen and were filled with granular or globular, deep-pink-staining, sharply circumscribed bodies which with Nile blue sulfate stained deep blue to purple. There were no vacuoles. Almost all of the tubules, both convoluted and collecting, were filled with casts composed most often of erythrocytes or polymorphonuclear leukocytes and less frequently of hyaline or amorphous material, hemoglobin or epithelial cells. The interstitial tissue showed some diffuse edema and marked congestion of the capillaries. There was a homogeneous sprinkling with polymorphonuclear leukocytes and lymphocytes, and less frequently condensations of these cells into small foci. None of the arteries or arterioles showed any sclerosis or obliterating endarteritis. Very occasionally a small or large arteriole disclosed an acute necrotizing arteriolitis which was strikingly similar to the lesion of periarteritis nodosa (Fig. 4). There were fibrinoid necrosis of the media, some proliferation of the intima but more of the adventitia, and a diffuse infiltration with polymorphonuclear leukocytes and occasional eosinophils and eosinophilic plasma cells. Some vessels in addition contained thrombi in their lumina. In a few arterioles the intima and media were normal but the adventitia and immediately surrounding connective tissue were diffusely infiltrated with cells of inflammatory origin. None of the vessels showed any evidence of healing. Many sections of each kidney stained with Giemsa's stain, and eosin and methylene blue, failed to show inclusion bodies or bacteria of any kind.

Histologic sections of the pelves and ureters were essentially similar. Although the mucosa was mostly denuded, the remaining nests of epi-

thelial cells were normal. There was marked edema of the entire wall, congestion of the capillaries and in the submucosa hemorrhagic extravasation in large areas. There was in addition a diffuse but light infiltration of all of the coats with polymorphonuclear leukocytes and a very occasional eosinophil or eosinophilic plasma cell. Many of the arterioles throughout the entire wall, but particularly the larger ones in the serosa, showed advanced necrotizing arteriolitis of the same nature as that found in the kidneys and previously described. Here, even more than in the kidneys, the degree of vascular involvement was out of all proportion to the amount of inflammation in the adjoining tissue. Sections of the urinary bladder were fundamentally the same as those of the ureters and pelves. There was, however, less sloughing of the epithelium, more extensive hemorrhage and much less inflammation. The arterioles in the outer portion of the wall showed necrotizing arteriolitis similar to, but less extensive than, that found in the kidneys, pelves and ureters. Sections of the lower urinary tract stained with Giemsa's stain, and eosin and methylene blue, as in the kidneys, failed to disclose inclusion bodies in the remaining epithelial cells or bacteria in any of the tissues.

Microscopic sections of the heart showed a uremic pericarditis composed of fibrin, mononuclear cells, a few polymorphonuclear leukocytes and proliferated mesothelial cells. There were no bacteria. The liver revealed focal areas of degeneration, some fatty metamorphosis and a moderate increase of cellularity about the portal radicles. Necrotizing arteriolitis was not found in any of the organs outside of the urinary tract.

DISCUSSION

Because the patient had been in perfect health before the vaccination, there is little doubt that the nephritis was directly related to this procedure. Only 37 days elapsed from the time of vaccination to the time of death, but the changes in the kidneys are entirely compatible with an illness of 5 weeks' duration. Experimentally, it has been shown repeatedly that rabbits develop clinical manifestations of nephritis 5 to 8 days after injection of nephrotoxic duck serum.² In the case reported here, back pain developed within 1 week after vaccination and, although the urine was not examined until 2½ weeks later, the nephritis was undoubtedly ushered in with the pain in the loin. Experimentally, it has been shown also that proliferative changes in the glomerular tufts and capsules are clearly evident by the sixth to eighth day after injection of nephrotoxic serum and that by the tenth day definite glomerular crescents are present. Thus pathologically, too, the

renal lesions as described are of such a nature that the available time is well beyond the minimal limit necessary for such changes to develop.

Today, thanks to vaccination, one does not see large epidemics of smallpox such as were prevalent at the turn of the century and before. The adequate post-mortem accounts of the fatalities in those epidemics, however, disclose a striking similarity between some cases of variola and the case of post-vaccination nephritis reported here. All authors agree that ordinarily variola produces no characteristic lesion in the kidneys. Lillie,³ in summarizing the renal changes which have been described, listed focal necrosis, interstitial nephritis of the type seen in scarlet fever, proliferation of the glomerular epithelium with degeneration of the tubules, degeneration of the tubules alone, acute suppurative nephritis and acute glomerulonephritis. He also stated that most observers have been unable to produce any changes in the kidneys of experimental animals. Councilman, Magrath and Brinckerhoff,⁴ in 1904, described 5 cases of acute glomerulonephritis encountered in 54 necropsies of variola which, as far as can be judged from their description, were very similar to the case described here. In one of these the duration of the disease was only 10 days. They further stated that: ". . . in both variola pustulosa hemorrhagica and in purpura variolosa there is extensive hemorrhage into the submucosa of the pelvis." In 1903, Perkins and Pay⁵ reported on 45 autopsies. Of the 3 subjects that had purpura, 2 showed marked hemorrhage into the submucosa of the pelvis. In 212 autopsies reported by Unruh⁶ in 1872, 28 showed hemorrhages into the pelves and, in most of these, also in the upper halves of the ureters. Twelve of the 28 patients had hemorrhagic variola while 16 did not. One case also showed hemorrhage into the urinary bladder. Microscopically the epithelium was intact, or denuded and distorted by the massive submucosal hemorrhage. The bleeding was thought to come from the engorged subepithelial capillary network and vessels of the mucosa. In his account Unruh did not speak of the presence or absence of either inflammation or arteriolitis. Finally Ponfik,⁷ in 1872, stated that hemorrhages may be present in the calices or pelves of the kidney, the upper halves of the ureters and the urinary bladder.

It is evident from this summary of the literature that, although consistent pathologic lesions do not occur in the urinary tract in all fatal cases of variola, those kidneys that do show noteworthy changes present a somewhat characteristic pattern. Briefly it may consist of a diffuse glomerulonephritis with massive hemorrhages into the calices and pelves of the kidneys, the upper halves of the ureters and occasion-

ally the bladder mucosa. These are precisely the lesions which occurred in the case of post-vaccinial nephritis reported here, except that in this case there was, in addition, severe necrotizing arteriolitis. Why the hemorrhages should be limited to the upper halves of the ureters is not at all clear. Because, however, the inflammatory process in the walls of the calices, pelves, ureters and bladder was relatively slight, and because necrotizing arteriolitis was, in contrast, very severe, the arterial lesions are considered as the cause of the massive hemorrhages. To draw the above comparison between the changes in the urinary tract of cases of variola and those of cases of vaccinia is not so far fetched as may at first glance appear, for there is at present much evidence which shows the close association of the viruses of variola and vaccinia and, in fact, that “. . . variola can be transformed into vaccinia.”⁸

Although there is no doubt that the diffuse glomerulonephritis in the case at hand was related to the vaccination, the exact mechanism involved is more difficult to ascertain. Today, all available evidence, both clinical and experimental, indicates that diffuse glomerulonephritis in general is an allergic response of the kidneys to some “toxin” and not a result of direct bacterial invasion.⁹ It is also well known that substances other than bacteria may be the causative agents. Thus, glomerulonephritis has been repeatedly produced in rabbits by the injection of nephrotoxic duck serum.² Rich and Gregory¹⁰ produced typical acute glomerulonephritis in sensitized rabbits by the injection of horse serum. Finally Reimann, Price and I¹¹ reported two examples of necrotizing arteriolitis and, later, chronic glomerulonephritis in patients with trichinosis, probably as a result of sensitivity to trichina protein.

Because the patient whose case is described in this report was vaccinated 30 years previously, it is assumed that sensitivity developed at that time and that the present vaccination resulted in an allergic reaction which seriously affected the urinary tract. Since each vaccine contained both calf serum and vaccine virus, it is impossible to be absolutely certain which was responsible for the sensitivity and the reaction. The appearance of a macular and then pustular rash, however, strongly suggests generalized vaccinia rather than serum disease. The failure to find inclusion bodies in the kidneys or in the rest of the urinary tract is not surprising for, drawing a parallel with other cases of diffuse glomerulonephritis, such renal lesions should be the result of sensitivity to the vaccine protein and not a direct action of the virus on these tissues. Recently, there have been several reports in the French literature¹²⁻¹⁴ of acute nephritis following vaccination for typhoid and paratyphoid A and B. Since recovery ensued in all cases, the type of

renal damage was not definitely established, although the clinical behavior in all cases was that of diffuse glomerulonephritis. This vaccine contained only dead organisms and no serum, and therefore the nephritis was undoubtedly due to sensitivity to bacterial proteins. Indirectly this adds credence to the contention that in the case described here the causative agent was most likely the vaccine virus.

There are at least three reports in the literature which indicate that various allergic reactions may sometimes follow vaccination for smallpox. One is a case of acute diffuse glomerulonephritis reported by Saldún¹ and already referred to. A second is a case of purpura developing 14 days after vaccination in a man, 23 years old, described by Heaton.¹⁵ A third instance is a case reported by McLure¹⁶ in which urticaria followed revaccination of a white girl, 5½ years old. The necrotizing arteriolitis observed in the present case is further evidence of the presence of hypersensitivity, although this, like the nephritis, could be due to either the serum or the vaccinia. In the kidneys such arterial lesions are well known in the late stages of very fulminating acute diffuse glomerulonephritis.⁹ They have also been described in other viscera by Helpern and Trubek,¹⁷ Baehr,¹⁸ and others. Experimentally, Rich and Gregory¹⁰ have produced both necrotizing arteriolitis and acute diffuse glomerulonephritis in sensitized rabbits by the injection of horse serum. Arteriolar degeneration and necrosis, but with little or no inflammation, have also been produced by Goldblatt¹⁹ and by Winternitz, Mylon, Waters and Katzenstein²⁰ by ligating the renal arteries in dogs.

Finally, one often sees cases of chronic diffuse glomerulonephritis as a terminal event without any previous knowledge of the existence of the process and with no known antedating infection.²¹ Purely on a speculative basis it seems possible that, because of the widespread practice of vaccination, some persons might develop subclinical diffuse glomerulonephritis which would not be apparent until years later. Lyttle²² has shown, by using the Addis technic, that the urines of patients with scarlet fever, from 8 to 45 days after the onset, show a quantitative increase of albumin, erythrocytes, pus cells, epithelial cells and casts. In other words, they have subclinical nephritis. By using the same technic it might well be that some patients revaccinated for smallpox would show similar changes in the urine.

SUMMARY AND CONCLUSIONS

1. A case, with necropsy, of acute to subacute diffuse glomerulonephritis following revaccination for smallpox is described in a white man, 64 years old. The literature contains only one other similar report.

2. Pathologically, in addition to typical renal changes of diffuse glomerulonephritis, there were extensive submucosal hemorrhages in the calyces, pelves, ureters and urinary bladder. The lesions in the urinary tract were very similar to some of those described in large epidemics of variola which occurred at the turn of the century.

3. The causative agent is thought to be a sensitivity to the protein of vaccine virus which was first received 30 years previously, although sensitivity to calf serum cannot be absolutely ruled out.

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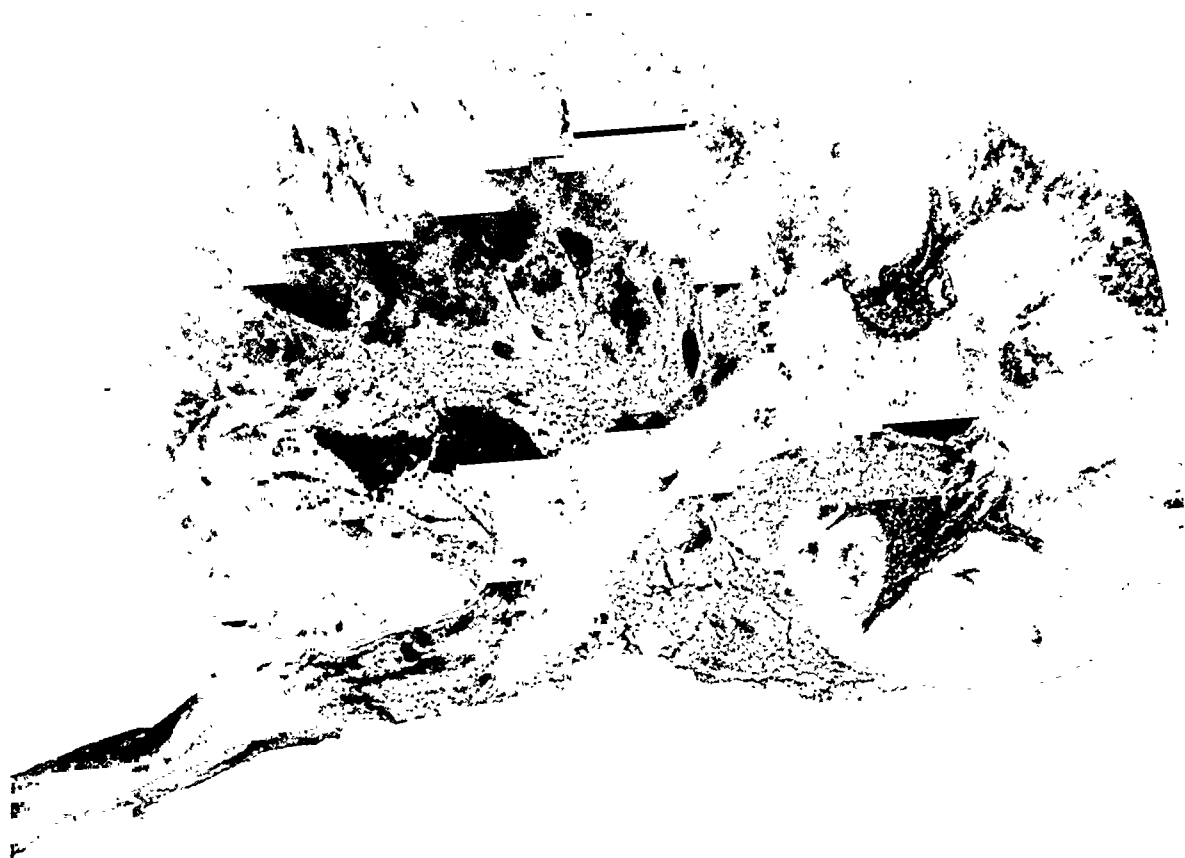
[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 186

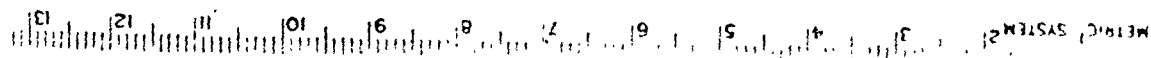
- FIG. 1. Cross section of a kidney showing a broad cortex and medulla; numerous petechiae; obscured corticomedullary demarcations and massive submucosal hemorrhages of the calices, pelvis and ureter.
- FIG. 2. Photomicrograph of a glomerulus showing a marked proliferation of endothelial and epithelial cells; a diffuse infiltration of the entire tuft with polymorphonuclear leukocytes; marked erythrocytic extravasation about the periphery of the glomerulus; edema and polymorphonuclear leukocytic infiltration of the interstitial connective tissue; dilated tubules; degenerated tubular epithelium and casts composed chiefly of erythrocytes and amorphous material. Hematoxylin and eosin stain. $\times 200$.

1

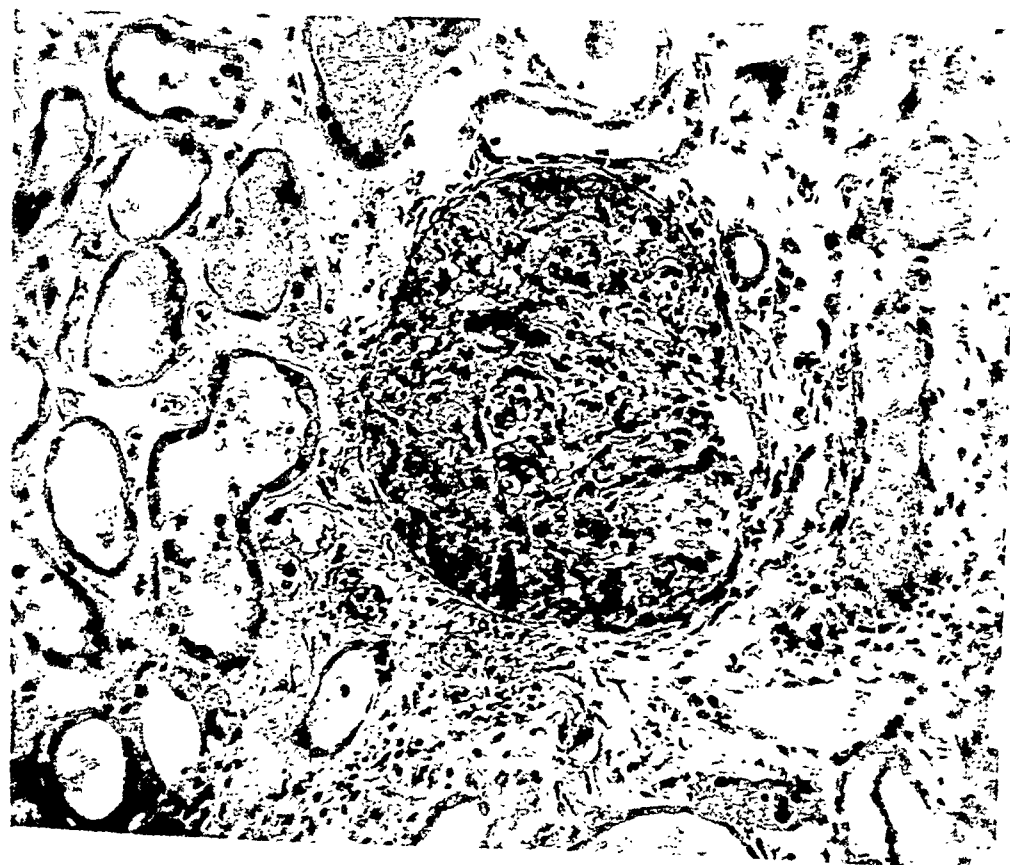


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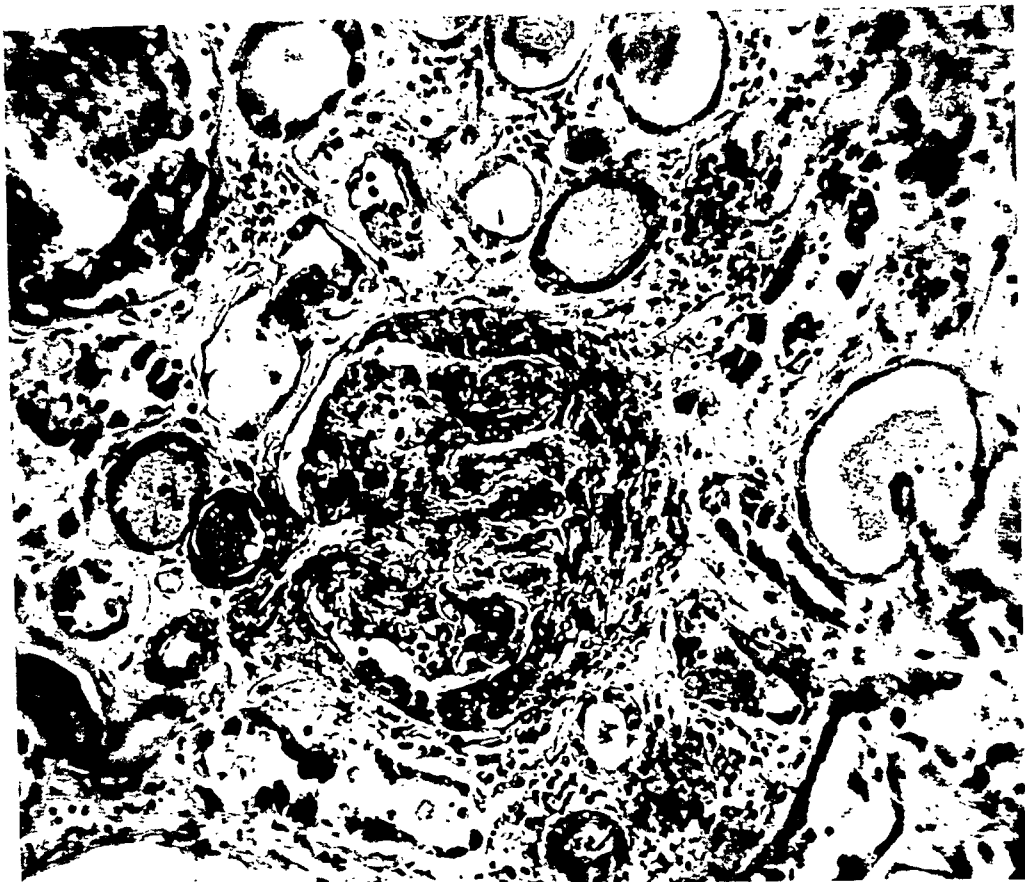
Glomerulonephritis Following Revaccination

PLATE 187

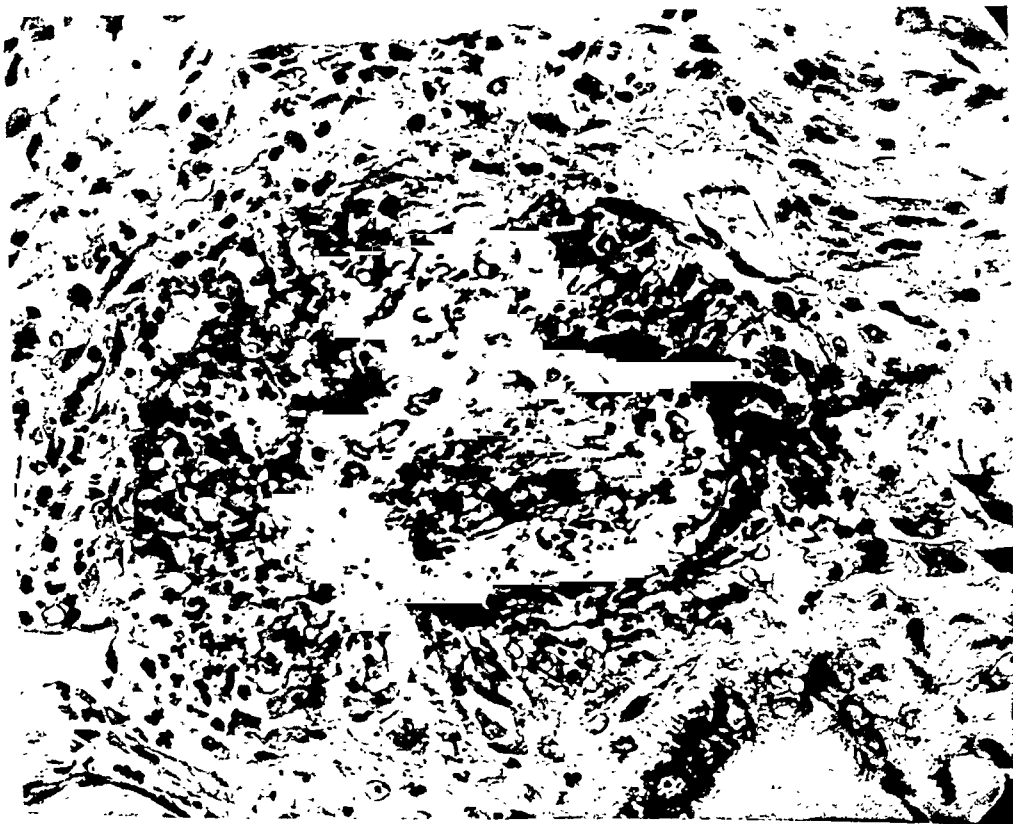
FIG. 3. Photomicrograph of a glomerulus showing essentially the same changes as in Figure 2 and in addition a well formed glomerular crescent. Hematoxylin and eosin stain. $\times 200$.

FIG. 4. Photomicrograph of a small renal arteriole showing intimal and adventitial proliferation; advanced fibrinoid necrosis of the media and a diffuse infiltration with polymorphonuclear leukocytes and scattered eosinophils and eosinophilic plasma cells. There is relatively slight inflammation of the surrounding connective tissue. Giemsa's stain. $\times 400$.

3



4



Herbut

Glomerulonephritis Following Revaccination

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THE MORPHOGENESIS AND SIGNIFICANCE OF DEGENERATIVE VERRUCAL ENDOCARDIOSIS (TERMINAL ENDOCARDITIS, ENDOCARDITIS SIMPLEX, NONBACTERIAL THROMBOTIC ENDOCARDITIS) *

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This paper is concerned with a lesion of the cardiac valves which has been variously labeled terminal endocarditis, marantic thrombosis, nonbacterial thrombotic endocarditis, endocarditis simplex, thrombo-endocarditis cachectica, etc. The valvular lesion has long been treated with a diffidence considered appropriate for a condition having no clinical significance. The alteration has been regarded simply as a bland thrombus deposited from the blood within a cardiac chamber onto a normal or thickened valve, the surface of which is either intact or superficially degenerated.¹⁻⁵ The cause of the condition has not been established but investigators have inconclusively implicated a variety of factors, including toxins, abnormal metabolism and a terminally sluggish circulation.

A minority point of view opposing the thrombotic concept began to take form when Neumann,⁶ in 1896, indicated that the thrombotic excrescence was in reality degenerated valvular collagen which histologically simulated fibrin. He therefore applied the term "fibrinoid" to this substance. Several years later (1903), Königer² conceded that the base of these excrescences was probably degenerated collagen but maintained that their major portion consisted of thrombotic deposits. Königer's has remained the prevailing concept.

In 1939, in a discussion incidental to an elucidation of the mechanism of localization of vegetations of bacterial endocarditis,⁷ attention was called to the valvular genesis of the verrucae of "terminal endocarditis." Repeated observations over the past 6 years have fortified the impression that these verrucae are not accretions of thrombotic material deposited onto valves but rather that they are composed of material derived from the valve itself. It is our opinion that this material con-

* Received for publication, January 10, 1944.

sists primarily and predominantly of swollen, degenerated valvular collagen with occasionally an admixture of varying amounts of plasma and blood-cellular elements which have exuded from the valvular vessels. Furthermore, we submit that the determination of the morphogenesis of these lesions is not a mere academic nicety inasmuch as we feel that they constitute the first stage in the sequence of events leading to the development, in many cases, of bacterial endocarditis.⁸ Because of this concept of the relationship of "terminal" to bacterial endocarditis it seems important to try to clarify certain histologic details and to integrate seemingly discordant facts into a unified, comprehensible picture. It is with this aim that we have undertaken a systematic study of the basic endocardial lesion generally designated as "terminal endocarditis."

MATERIALS AND METHODS

There were available for study the clinical histories, gross specimens and microscopic preparations of 66 cases in which there was no evidence of bacterial endocarditis or of acute rheumatic carditis. Of these, 50 cases had active lesions of "terminal" endocarditis; the remainder were examples of healed lesions. The criteria for evaluating activity are outlined below. Multiple sections from each heart were examined and, in certain indicated instances, six sections were taken according to the procedure of Gross, Antopol and Sacks.⁹ However, in every case, sections of the base of the heart (M.V.P.)* were included.†

The tissues were fixed in a 20 per cent Formalin (8 per cent formaldehyde) solution except for one case in which Zenker's solution was used. The stains included hematoxylin and eosin, the Mallory-Heidenhain azocarmine, Mallory's phosphotungstic acid hematoxylin, van Gieson's combined with Weigert's, and the silver stains of Wilder and of Bielschowsky as modified by Foot. In addition, the lesions of 3 cases were subjected to serial digestion with trypsin following which they were treated with van Gieson's stain. In three instances, serial sections 6 μ thick were cut.

FINDINGS

Relationship to Malignant Tumors. "Terminal endocarditis" has been considered to be associated with patients dying of malignant tumors. In our small series, such neoplasms were present in 28 per cent

* M.V.P. = Mitral valve posterior.

† In this connection, Gross's own investigation⁹ indicates that the incidence of Aschoff bodies in rheumatic hearts could have been determined from the examination of the two sections from the base of the heart only, inasmuch as no additional cases with Aschoff bodies were discovered by the study of the four remaining sections.

of 50 cases (Table I). This incidence appears strikingly high and yet, in the general autopsy material of the hospital, 23 per cent of 2000 patients died with malignant tumors. If there were no selection of patients with malignant growths by terminal endocarditis, cancers would be expected to occur with the same frequency in our 50 endocardial cases as in the general post-mortem material, namely, 23 per cent. This was essentially true inasmuch as the difference between 28 and 23 per cent is so small that when subjected to the X^2 test of statistical significance, a positive correlation between patients with malignant tumors and those with "terminal endocarditis" was not dem-

TABLE I

Cause of Death in 50 Unselected Cases of "Terminal Endocarditis" (Active)

Cause of death	No. of cases
Malignant tumor	14
Congestive heart failure	10
Major operation	7
Pneumonia	4
Acute and subacute glomerulonephritis	2
Pulmonary embolus	2
Acute suppurative pyelonephritis	2
Congenital polyposis	2
Ulcerative colitis	2
Blood dyscrasia	2
Coronary occlusion	1
Periarteritis nodosa	1
Congenital heart disease	1
Total	50

onstrated. Additional information of the same order would have been furnished by the converse data; namely, the comparative incidence of "terminal endocarditis" among a large series of patients with cancer, pneumonia, glomerulonephritis, and other conditions. These data are not available at present.

Association with Acute Diseases. Of great significance is the fact that these endocardial lesions are found in persons who have died after an illness of only a few days' duration; for example, in patients dying of pneumonia or following a recent operation (Table I). In other words, the lesion does not require the background of a long, wasting disease. Furthermore—and this is of great importance—the lesion may accompany diseases which are by no means always fatal. That is to say, inasmuch as "terminal endocarditis" occurs in patients with pneumonia, nephritis, and other diseases which often are not fatal, it is reasonable to presume that "terminal endocarditis" may occur during the course of diseases which the patients may survive for years. This

fact is of prime concern in connection with the subsequent superimposition of bacterial endocarditis, a point which will be elaborated further.⁸

Age and Sex Incidence. In this small series, 70 per cent of the cases of "terminal endocarditis" occurred in persons above the age of 40 (Table II). This does not indicate a selectivity for the older age group inasmuch as 67 per cent of all those in the general autopsy material of the hospital were in the same age group. The difference between 70 and 67 per cent is not statistically significant. Similarly, 46 per cent of our cases occurred in females and 54 per cent in males. The corresponding distribution of sexes in our autopsy population is

TABLE II
Age Distribution of "Terminal Endocarditis" (Active)

Decade	No. of cases
1-10	1
11-20	7
21-30	2
31-40	5
41-50	8
51-60	11
Above 60 years	16
Total	50

41 and 59 per cent respectively. The difference between these sets of figures, again, is not beyond the range of chance variation as determined by the X^2 test.

In summary, it appears from an analysis of our material that the lesion of "terminal endocarditis" occurs in random distribution at all ages and in both sexes as well as in a great variety of diseases, both acute and chronic, with possibly a very slight tendency to favor those patients with malignant tumors, although statistical proof thereof is lacking.

Distribution of Lesions. In 34 of our 50 active cases (68 per cent), the lesions occurred on valves that were thickened by chronic rheumatic valvulitis. In 12 of the remaining cases the valves were moderately sclerotic but rheumatic cardiac stigmata were absent. The valves of 4 cases were apparently normal except for "terminal endocarditis."

The distribution of the valvular lesions of "terminal endocarditis" parallels fairly closely that observed in rheumatic and bacterial endocarditis. The mitral valve was involved most frequently and with about twice the frequency of the aortic valve. The right side of the heart was rarely the site of a lesion and, in this series, the pulmonic valve was spared. In six instances, lesions were found on two valves of the same heart.

GROSS EXAMINATION

It is generally assumed that the lesion of "terminal endocarditis" is a single, small verruca. However, the lesions may assume a wide range of gross patterns, including those of rheumatic and bacterial endocarditis, so that differentiation by inspection may be impossible in some instances. In general, the lesions have one of five patterns:

1. The small univerrucal type. This group consists of lesions that are barely visible, or measure up to about 3 mm. in height. They are light gray-brown to dark brown and usually firmly attached to the valve as if a part thereof rather than a superficial deposit. These are practically always found on previously thickened fibrotic valves. They are seen characteristically at the line of closure. On the aortic valves, the corpora arantii are especially vulnerable, quite as in rheumatic or bacterial valvulitis. (The term "univerrucal" is applied also to those valves with two or three verrucae in which the lesions are isolated, as in Figs. 1 and 2.)

2. The large univerrucal type. These are tawny, usually very finely granular and firmly adherent to the valve proper (Fig. 2). In unusual instances, they are so decidedly shaggy as to make gross differentiation from bacterial endocarditis a mere guess. In other instances, the surface may be smooth and the lesion soft and polypoid. This latter form is found usually to differ histologically from the preceding type.

3. The small multiverrucal type. These lesions are about 3 mm. in diameter, firmly attached to the valve and arranged in a fairly regular, beaded ridge along the line of closure. They may be macroscopically indistinguishable from acute rheumatic verrucal endocarditis. As a rule, however, they are larger and somewhat more friable than rheumatic verrucae. They may, in some cases, suggest bacterial endocarditis but their relative regularity, especially over a large span of the valve, would militate against this diagnosis.

4. The large multiverrucal type (Figs. 3 and 4). This is a striking lesion composed of soft, friable masses beaded along the line of closure for as much as 4 to 5 cm. and measuring up to fully 6 to 7 mm. in height. The verrucae may be as large as many of the vegetations of bacterial endocarditis, but, unlike them, are characterized by a remarkable regularity in size, consistency, color and contour. They may be loosely attached to the valve and when removed may expose an endocardial surface that is only slightly roughened. Such lesions, although nonbacterial, are prone to produce emboli. They generally show a characteristic histologic picture to be described as the "exudative" type.

5. Healed type. Inasmuch as "terminal endocarditis" is seen post-operatively and in cases of pneumonia, glomerulonephritis, etc.; that is,

in diseases not necessarily fatal, it appears plausible that, if the patient survives, the verruca formed during the period of illness will either resolve or become a fibrous tab or nodule, or a focal, slightly bulbous thickening of the edge of the valve. Such changes are found commonly near the free edge of the valves, particularly at the corpora arantii (Lamblian excrescences*) or along the adjacent ridge (Figs. 5 and 6). They are 1 to 5 mm. in length, are covered by smooth endothelium and have the color and consistency of the valve to which they are attached. The "healed" lesions in this study occurred on non-rheumatic valves in 11 cases and in 5 instances on valves that showed evidence of chronic rheumatic inflammation.

MICROSCOPIC EXAMINATION

The histologic patterns of the active lesions appear to fall into two principal groups, differentiated primarily by the amount of degenerated collagen present in the verrucae:

Degenerative Type

The histologic picture characterizing the degenerative type commonly corresponds to the small or the large, granular, densely adherent univerrucal gross type (Fig. 14). It begins as a focus of granular, eosinophilic degeneration in the outer layers of the valve, generally near the free margin (Fig. 13). As a rule, the auricular surfaces of the A-V valves and the ventricular surfaces of the semilunar valves are those selected. This alteration may occur without a grossly visible change in the contour of the valve and hence is often overlooked, as might have possibly occurred in the lesion illustrated in Figure 13. As in any other organ, the altered collagen is appreciably more acidophilic than the adjacent uninvolved collagen. The original focus enlarges and the altered fibers swell and become loosened and fragmented to form a mound of degenerated, soggy appearing collagen. Here and there, small foci of precipitated serum, fibrin, or platelets are observed, as if there had occurred a slight seepage from permeable or eroded valvular vessels. Occasionally, several clumps of red blood cells and leukocytes of various kinds are present, not only in the verruca, but near the verrucal base and obviously within the valve proper. In practically all instances of this type there is no abrupt demarcation of the verruca from the valve; rather, one observes that the eosinophilic, fibrillar, or granular material of the verruca represents the termination of the valvular fibers which fray out into the lesion. To be sure, the

* Lambl. Papilläre Excrescenzen an der Semilunar-Klappe der Aorta. *Wien. med. Wchschr.*, 1856, 6, 244.

acidophilic alteration may occasionally be seen in the fibers of the valve itself even at a distance from the verruca. With serial sections, it is found that this alteration may occur in the fibers well within the valve, which may or may not be in continuity with the surface, so that the possibility of its representing imbibed thrombotic material from the cardiac chamber would seem to be most unlikely.

With carefully controlled Mallory-Heidenhain stains, there is observed in some instances ragged, ripped, anuclear, collagenous fibers in all parts of the verruca, including its most superficial portion. The absence of fibroblasts about such torn, displaced fibers distinguishes them from fibers formed as a result of a reparatory process. However, fibroblasts and even granulation tissue may be seen in other parts of the verruca, especially at its base, but such foci are easily distinguishable from the degenerated areas. The altered fibers stain various shades of red, orange, or blue, depending on the degree of degeneration. They may resemble fibrin tinctorially but they usually can be distinguished by such structural details as sharpness of contour, the irregular, torn ends, and often by continuity with a collagenous fiber of the valve itself. Indeed, a few foci of fibrin and platelets may be included but most of the granular, platelet-like or fibrinoid substance appears to be derived from collagen. This altered collagen differs from platelets and fibrin, in part by its relative resistance to tryptic digestion, but also by its relationship to disintegrating collagenous fibers which shade off finally into the granular platelet-like debris. In other words, the granular material constitutes an advanced stage of degeneration. One frequently observes an identical change in the dermal lesions of granuloma annulare, for example, or in the subcutaneous rheumatic nodules, in which there is no question that the fibrinoid and platelet-like material are truly products of altered collagen. This feature is illustrated in Figure 15. Additional evidence that this material is not fibrin or platelets is furnished by silver stains and tryptic digestion.

Silver Stain. With silver stains by either the Wilder or Foot modification of the Bielschowsky technic one finds that the quantity of argyrophilic fibers in the lesions varies considerably. In some lesions, they are entirely absent; in others, there are so many closely lamellated argyrophilic fibrils that the verrucae appear almost solidly impregnated. Usually, one observes foci of irregular, anuclear, fragmented fibers, some of which are as fine as reticulum and others fully as thick as ordinary collagenous fibers (Fig. 17). The fibers to which we are referring are, of course, entirely removed from the reticulin of the granulation tissue that may be present at the base of the verruca.

Tryptic Digestion. Unfortunately, there is no stain that will un-

equivocally differentiate all forms of altered collagen from fibrin. We have therefore made use of the digestion of the lesions with trypsin, a procedure dependent on the differential digestive properties of trypsin, which were found informative in previous studies on hyaline material in tumors,¹⁰ in renal glomeruli¹¹ and in the investigation of so-called aortic thrombi.¹² It is known that trypsin digests collagen with difficulty whereas, on the other hand, clots of platelets and fibrin are easily digestible. We, therefore, determined the relative digestibility of the substance composing the verrucae. The procedure included placing a paraffin section (6 μ thick) of the verruca and a section of blood clot on the same slide. Serial sections were placed in a 0.3 per cent solution of fresh trypsin alkalized with 0.03 per cent Na_2CO_3 to which chloroform had been added as a preservative. The tissues were then digested for 1 hour at 37°C., after which a slide was removed approximately every half hour for a period of about 3 hours and stained with van Gieson's stain. This time period permitted definite differential digestion of the fibrin and platelets, the verrucae, and the valvular collagen. The order of the rapidity and ease of digestion was as follows:

1. Fibrin and platelets: early and complete digestion
2. Verruca: digested partially and at a later period
3. Collagen of valve: practically undigested during the period of exposure

Exudative Type

The exudative type of verruca occurs relatively uncommonly, having been found in about 10 per cent of our lesions. These verrucae may vary greatly in size but are especially characteristic of the large multiverrucal, soft, friable lesions (Figs. 3 and 4).

They are made up principally of material that superficially seems indistinguishable from serum, platelets and fibrin (Figs. 7 and 8). With the Mallory-Heidenhain stain, one may observe in most of them several haphazardly arranged, blue, isolated, collagenous fibers, again unassociated with fibroblasts and not part of a reparatory process. Similar fibers may be seen with silver stains. In addition, these lesions may contain a few red blood cells, an occasional focus of polymorphonuclear leukocytes, and a few lymphocytes. The components of this type of verruca are as a rule arranged in a completely irregular pattern of clumps of varying size and do not suggest successive accretions of deposits of thrombi. In each instance there is evidence of fibrinoid degeneration of the valve at the base of the verruca.

No elastic tissue is found in these lesions. The tryptic digestion fails to reveal any noteworthy difference between this type of verruca and the fibrin of clots.

Healed Type

As stated, this lesion consists of a fibrous tab, nodule or focal collagenous thickening with rarely a few elastic fibers. Such a lesion may itself undergo degeneration and become the site of a verruca which is practically always of the degenerative type (Fig. 19). In valves thickened by chronic rheumatic inflammation there are no histologic features that distinguish the healed verruca of "terminal endocarditis" from that of acute rheumatic valvulitis.

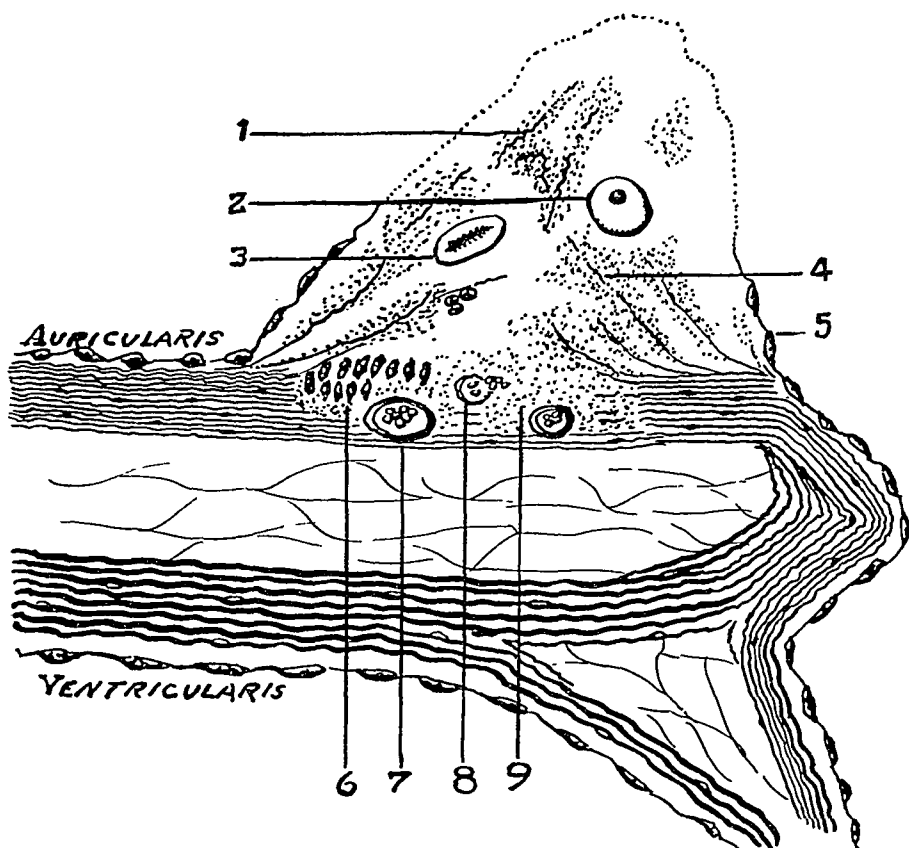
Cellularity of the Verrucae. In the majority of the verrucae no cells, or merely a few shrunken degenerated cells and pyknotic nuclei, are present. In most of the remainder, one sees loosely scattered histiocytes in addition to the degenerating cells, although, occasionally, clumps of polymorphonuclear leukocytes and isolated lymphocytes are seen. In many instances a few foam cells, filled apparently with lipoids, are included in the body of the lesion. In one instance the abundance of these vacuolated cells well within the verruca presented a striking picture (Figs. 10 and 11). Isolated Anitschkow myocytes (myocardial reticulocytes) were observed in the midst of the fibrinoid material in the body of two of the verrucae (Fig. 9). As a rule, there is greater cellularity in the lesion of exudative type than in that of degenerative type (Figs. 7 and 8). The reaction within the portion of the valve forming the base of the lesion was negligible in about one-half the cases but in the remainder took one of two patterns: (1) In some instances, the normal fibrocytes of the valve developed swollen, hyperchromatic nuclei so as to resemble newly formed active fibroblasts; (2) in other cases, there was an actual increase in number of fibrocytes or fibroblasts arranged vertically or obliquely in the direction of the verruca as if some tropism were guiding them toward the lesion. Indeed, in several instances, there was observed actual palisading of the cells in a pattern indistinguishable from that regarded as characteristic of rheumatic valvulitis (Fig. 8). In these cases, the reaction was limited strictly to the base of the verruca and there was no associated inflammation of the valvular ring or interstitial valvulitis. Furthermore, no Aschoff bodies were found in any of these cases notwithstanding the use of the method of section advocated by Gross.⁹

Changes in the Myocardium and Other Organs. Search was made for changes in the remainder of the heart and other organs which might possibly be related to the valvular lesion. We were especially interested in collagenous alterations, vascular lesions and emboli. Focal collagenous granular alterations were found in the walls of small arteries and arterioles of the myocardium in 5 cases, each in association with granu-

lar verrucae in the lumen at the site of alteration. These granular verrucae or "plugs" project into the lumen as knobs or as irregular lobulations. They have been variously described as platelet thrombi, as swollen, desquamated endothelial cells and as emboli from verrucae. They may become organized and canalized. These luminal projections have been observed frequently and their occurrence stressed in acute disseminated lupus erythematosus and in the entity described by Gross and Friedberg⁵ as "nonbacterial thrombotic endocarditis." Because of association with, and apparent emergence from, a site of granular degeneration in the vessel wall, they appear actually to be fibrinoid, verrucal swellings of portions of the vascular wall.¹³

Occasionally, portions of verrucae, particularly of the more friable exudative type, break off to produce infarcts, and, rarely, even a fatal encephalomalacia.

In summary, the lesions of "terminal endocarditis" are observed grossly as single or multiple verrucae, or as healed, smooth, projecting



Text-fig. 1. Schematic drawing of the composite features of nonspecific verrucae: 1 = fragmented, anuclear collagenous and argyrophilic fibers displaced from the valve into the verruca; 2 = foam cell; 3 = Anitschkow myocyte; 4 = granular disintegration of valvular collagenous fibers; 5 = valvular endothelium which has been raised and disrupted by the verruca; 6 = reactive histiocytes; 7 = arteriole; 8 = eroded arteriole; 9 = granular disintegration of collagen within original limits of valve.

tabs, nodules, or focal thickening of valves. Microscopically, they may be divided into three types: the degenerative type, consisting preponderantly of altered, swollen valvular collagen; the exudative type, made up of platelets, serum, fibrin and usually a few fragments of disrupted collagenous fibers; and the healed type representing fibrosis of an active verruca. Of these, the type consisting almost entirely of degenerated collagen occurs with about ten times the frequency of the other form of active verruca.

COMMENT

Morphogenesis

We have thus far presented the histologic details of the nonbacterial verrucae. It is our impression that these observations indicate an origin of the verrucae from the valve. That is to say, we regard the verruca as a focus of degenerated, loosened, swollen, valvular collagen, occasionally puffed out with more or less exuded plasma from the permeable or eroded vessels of the valve itself. However, those who do not distinguish the verrucae from simple thrombi deposited by the blood streaming over the valve, maintain that the collagenous and argyrophilic fibers on which we have laid much stress are observed in ordinary vascular thrombi. They regard the altered verrucal collagen, or fibrinoid, as identical tinctorially with the fibrin of thrombi, and hence conclude, in effect, that verrucae and thrombi are not only indistinguishable but represent essentially the same pathogenetic process.

Verrucae do often closely resemble thrombi in sections stained merely with hematoxylin and eosin. Furthermore, collagen and argyrophilic fibers, and of course platelets and fibrin, are found in vascular thrombi and obviously are not *per se* peculiar to the verruca. But to conclude from this fact that the verruca is a thrombotic deposit is to disregard a fundamental distinction between degeneration and repair. It is to be emphasized that this distinction may be easily missed in a section stained with hematoxylin and eosin, and yet it is on just such routine sections that the general concept of the thrombotic nature of verrucae is based. The verrucal collagen to which we refer has undergone various degrees of degeneration so that with the hematoxylin and eosin stain it appears deeply eosinophilic, anuclear, and occasionally fragmented and granular, thereby closely resembling fibrin and platelets. However, this same degenerated camouflaged material may retain sufficient tinctorial properties of collagen to reveal its identity with appropriate stains. For example, it may show a partial affinity to aniline blue as well as to silver (Fig. 17). In other words, with a

differential stain, one may observe a fiber of valvular collagen continue up into verruca and within the body of the verruca exhibit a gradual loss of affinity for aniline blue and, *pari passu*, a progressively increased azocarminophilia, the latter indicating degeneration of the terminal portion of the fiber. The degenerated anuclear fibers may be fragmented, disrupted and scattered to various parts of the verrucae.^{14, 15} This pattern is quite unlike the radiating, more orderly picture of organization within a thrombus, be it in a vein, artery, or cardiac chamber (Fig. 16).

The masking of collagen and its argyrophilic derivatives is a commonplace phenomenon which can be observed in a variety of organs; *e.g.*, in the degenerated foci of granuloma annulare of the skin, in synovial degenerations, in Aschoff nodules, etc. The fact is that one could superimpose many of the verrucae onto the lesions of granuloma annulare, for example, and differentiation of the verrucal material from the areas of cutaneous fibrinoid alteration would be impossible. It therefore appears that the fundamental interpretive discrepancy of those who believe in the thrombotic nature of the verrucae is that they ascribe the origin of the collagen in the verrucae—*i.e.*, the fibrinoid collagen “uncovered” by special stains—to the process of organization notwithstanding the unquestionable lack of evidence of organization in the foci in question in sections stained with hematoxylin and eosin.

Some observers, in order to account for the argyrophilic fibers in fibrinoid material,¹⁶ maintain that serum may seep in through the surface and separate the collagenous fibers into thin fibrils, and that these fibrils by virtue of their thinness acquire an affinity for silver. The evidence from the current studies does not support this combination of assumptions. In the first place, serial sections reveal foci of degenerated collagen with argyrophilic fibers well within the valve and showing no continuity with the surface. Indeed, occasionally such degenerated areas are seen in valves with intact endothelium. It is hardly likely that serum from the cardiac chamber has soaked through an intact valve to collect as a pool within the body of that valve. Furthermore, there were found in the verrucae, degenerated collagenous fibers which were argyrophilic *and yet were distinctly thicker* than the fine collagenous fibers in the same sections that manifested no affinity for silver (Fig. 17). In addition, there can be observed, in some of the verrucae, dense, compact masses of argyrophilic fibers which were tightly apposed and obviously not produced by a separation of pre-existing collagenous fibrils. Therefore, it would appear that the view that the argyrophilic fibers of verruca arise through cleavage of collagen by serum is not supportable.

In some cases, the degeneration of valvular collagen was accompanied by a cellular reaction; in others it was not. We are unable to agree that the absence of cellular reaction precludes the fibrinoid material being degenerated collagen.¹⁰ Witness, for example, the bland degeneration of collagen within sclerotic valvular rings, sclerotic arteries, or within the collagenous capsule of a chronic tuberculous focus. In each of these sites there is frequently no noteworthy "exudative response" to the presence of appreciable degenerated collagen.

The reason for the presence of a cellular response in some of the verrucae and not in others is not entirely clear. However, it would appear that some of the basic factors concerned are the degree of valvular sclerosis, vascularity and cellularity preceding the formation of a verruca. That is to say, if a valve is thickened by dense nodules of practically acellular and avascular collagen, significant cellular response to an irritant is not to be anticipated. In much the same sense, there is less likely to be an exudative response to an irritant in a torpid, sclerotic, acellular, and avascular scar anywhere else in the body.

The resistance of most of the verrucae to trypsin is additional evidence that the fibrinoid material of the verrucae is of a composition different from thrombi. This principle has been confirmed in a study of so-called mural thrombi of the aorta.¹² Of further interest is the presence of myocytes and lipoid histiocytes in the verrucae (Figs. 9 and 10). Anitschkow myocytes¹⁷ are easily recognized cells found only in the heart. If myocytes are found within a verruca, it is to be presumed that the latter arose from the valve since myocytes are not known to circulate within the blood stream. To be sure, this presumption may be somewhat countered by the objection that the myocytes may have migrated into the thrombus from the valve. However, there is no evidence for such migration inasmuch as myocytes have not been found in mural thrombi located, for example, in auricular appendages or ventricles. The presence of foam cells within the body of unorganized verrucae constitutes additional evidence for the valvular genesis of the lesions. Foam cells are frequently associated with degenerated collagen in the heart as well as other organs, sometimes in striking concentrations. However, this latter bit of evidence must remain merely presumptive inasmuch as such cells are found occasionally within vascular and mural thrombi.

As a final word in the accumulation of evidence against the thrombotic concept of verrucae, it is to be pointed out again that the velocity and momentum of the blood in the heart and arteries would seem to operate against the deposition of thrombi.^{7, 15} The factors of stasis, eddy currents, and a sluggish circulation with the pressure of venous

blood, more or less predispose to the deposition of thrombi. Such factors are of concern in the auricular appendages in fibrillation, in the pockets of valves, or in the ventricles following infarction; but it would appear that they are reduced to relative insignificance along the auricular surface of the mitral valve and the ventricular surface of the aortic valve—sites of verrucal formation—as the blood in the chambers cascades past these surfaces.⁷

In summary, we submit that the evidence is strongly in favor of the valvulogenic rather than the thrombogenic nature of the verrucae. This evidence is based on identification: (1) by special stains of much of the fibrinoid material as altered collagen; (2) by the relative resistance to trypsin of the fibrinoid material as contrasted with fibrin; (3) by the presence in the verrucae of myocardial Anitschkow myocytes and lipoid macrophages, the former never found in the peripheral blood or thrombi. These various contrasts between verrucae and thrombi obtain irrespective of their location, be it vein, artery, aorta, or cardiac chamber. However, there were found a few instances of verrucae composed essentially of serum, platelets and fibrin and a few blood cells, rather than primarily of altered collagen. It is our unproved impression that even these are essentially coagula which are derived from the exudate of permeable or eroded *valvular* vessels and have clotted on the surface of the valve very much as plasma clots on abraded skin, or, to use a homely simile, as albumin coagulates on and adheres to the shell of an egg that has been cracked while in boiling water.

Pathogenesis

We are not certain why a portion of a valve undergoes degeneration and forms a verruca, but in searching for the possible agents we regard it as likely that several factors may be involved and that the phenomenon is the product of the effects of one or more of the following: (1) allergy; (2) vitamin C deficiency; (3) hemodynamic trauma to the valves; and (4) the existence of abnormally thickened, sclerotic valves.

Allergy. Many investigators have repeatedly attributed the fibrinoid degeneration of collagen—especially the collagen of valves and arteries—to the effects of allergy.¹⁸⁻²² The fibrinoid change in many of the verrucae in our cases appears to be identical with that attributed to altered tissue reactivity. The nature of the allergens in these cases is not known, of course, although the possibility of bacterial proteins is a distinct one. At any rate, at least the adjuvant rôle of allergy in the production of fibrinoid degeneration is to be considered. This is not to say that all fibrinoid degeneration of the valves is on the basis of allergy. In many instances, the fibrinoid alteration seems to represent a

form of degeneration of valvular collagen in which allergy plays no conceivable rôle. This is very likely true of the more markedly thickened sclerotic valves. Certainly, the following additional factors must be weighed and placed properly in the scheme as a whole.

Vitamin C Deficiency. In recent years, emphasis on the relationship of vitamin C depletion to degeneration of collagen, especially of the collagen of cardiac valves, has been revived. Briefly, this association is suggested by the following evidence (although isolated data to the contrary have been recorded): first, the degeneration of collagen in various organs of scorbutic guinea-pigs; ^{23, 24} second, the fibrinoid valvular changes observed in scorbutic guinea-pigs; ²⁵⁻²⁷ third, the positive relation of ascorbic acid to the formation of collagenous fibers *in vitro* and *in vivo*; ^{28, 29} fourth, the evidence that vitamin C deficiency affects the cohesion of endothelial cells; ³⁰ fifth, the many observations that the collagenization of wounds is interfered with in vitamin C-deficient animals; ³¹ and finally, the tendency toward depletion of vitamin C in patients with fevers, intestinal diseases, neoplasms, postoperative periods, etc.³²⁻³⁵ In accord with this evidence, many of our patients might be judged to have been deficient in vitamin C and to have been subject to the effect of such depletion as the evidence mentioned above might indicate. The reason for the absence of generalized collagenous alteration in our cases may have been due to the relatively minor degree of depletion of vitamins and to the selective predisposition of the valves to such alteration.⁷ It is conceivable that other dietary deficiencies may play a part, but, as with vitamin C deficiency, it is likely that their damage is wrought in an important measure by abetting the degeneration of valvular collagen.

Hemodynamics and Sclerotic Valves. Probably a great factor in the predisposition of the valves to degeneration as compared with collagen elsewhere lies in their strategic situation which allows concentration of the continual hemodynamic impact by the blood stream against the valves. This selective "hemodynamic pounding" constitutes, in our opinion, the third and, as a rule, the principal factor in the degeneration of valvular collagen. The details of the dynamics are judged to be quite the same as those described previously in the explanation for the localization of vegetations of bacterial endocarditis.^{7, 15} In brief, a "line of closure" of a previously thickened valve—and the valves on which verrucae are found are usually thickened by fibrosis—is particularly predisposed to the systolic impact of the blood stream because it tends to obstruct rather than to "give way" with the stream. In addition, this site offers great frictional resistance to the current in proportion to the degree of stenosis. The contact of the so-called line

of closure with the current of blood is further enhanced as the regurgitant stream returns through the incompetent valve. The generally accepted explanation for the localization of lesions at the "line of closure" is that this site is traumatized as the cusps slap shut. However, it is germane to point out that if a valve is stenotic, the cusps are simply unable to impinge against each other; rather, the blood impinges against the cusps.⁷

It is obviously hazardous in a particular case to presume to estimate which one of the four factors or what combination of factors operated to produce the lesion. However, it seems not unreasonable that a verruca which has provoked cellular exudation and proliferation at its base and occurs in a thin or only slightly thickened valve is more likely to be the result of a hyperergic reaction than a bland verruca occurring in a markedly sclerotic valve. In the latter instance, hemodynamics are much more apt to have played the principal rôle.

Nomenclature

These verrucae have hitherto been regarded as terminal endocarditis, nonbacterial thrombotic endocarditis, marantic thrombosis, etc. In the current study, it has been shown that the lesions occur during acute as well as chronic illnesses, in the young as well as the aged, in the well nourished and in the marantic. In other words, the evidence indicates that the lesion may occur in a variety of illnesses which the patient may survive for years, presumably with subsequent healing of any verrucae that may have formed during the illness. Therefore, the designations "terminal" and "marantic" are unjustified. Furthermore, it appears quite possible that bacterial proteins may play a rôle in the production of the lesion, so that the qualification "nonbacterial" may not be strictly accurate, although it is understood that the term implies the absence of bacteria within the verrucae. In addition, evidence against the thrombotic nature of the lesion has been presented herewith so that, in our opinion, the designation "thrombotic" is inapplicable. Finally, because it appears to us that valvular degeneration rather than inflammation is generally the major element in the formation of these verrucae, we should prefer to consider them as primarily degenerative rather than inflammatory.

Therefore, the term "degenerative verrucal endocardiosis" * is pro-

* Because of the prevalent misunderstanding of the complete meaning of the suffix "osis," the following definition is quoted from *Webster's New International Dictionary of the English Language*, ed. 2, unabridged. G. and C. Merriam Co., Springfield, Mass., 1938, p. 1726:

-osis; pl.-oses. [fr. Gr.-osis, as in metamorphosis] A suffix signifying:

1. a. Condition, state, process, and the like, as in *hypnosis*, *psychosis*, *osmosis*; specif.,

posed to designate a nonspecific endocardial alteration, verrucal in appearance when fully developed, and occurring in association with a great variety of diseases, both acute and chronic, including those clinical entities designated by Gross and Friedberg⁵ as "nonbacterial thrombotic endocarditis." The verrucae in this latter condition are considered to be as nonspecific a component of the morphologic picture as is leukocytosis, for example, in many clinical syndromes.

Differentiation of Degenerative Verrucal Endocardiosis from Acute, Recurrent, Rheumatic Valvulitis

It is to be pointed out that inasmuch as the lesions of degenerative verrucal endocardiosis are prone to occur on valves fibroblastically thickened by rheumatic infection, the nonspecific verruca may erroneously be regarded as evidence of an acute exacerbation of a chronic rheumatic valvulitis. It may be impossible to establish the diagnosis by gross inspection. The differential diagnosis may be further complicated by the observation of palisaded histiocytes at the base of the verruca. This pattern of cellular proliferation is regarded as characteristic of the rheumatic lesion by Leary.³⁶ However, the observations made in the current study support those of Jaffé³⁷ who indicated that palisading of histiocytes may occur in nonspecific lesions. The absence of Aschoff bodies and of a diffuse interstitial valvulitis or, at the least, of a diffuse cellular reaction along much of the valvular surfaces, particularly the spongiosal surface, serves to differentiate degenerative verrucal endocardiosis from acute rheumatic valvulitis.

Differentiation of Degenerative Verrucal Endocardiosis from Bacterial Endocarditis and Atypical Verrucous Endocarditis

Grossly, a small proportion of the lesions, especially those of the multiverrucal type (Figs. 3 and 4), may simulate acute or subacute bacterial endocarditis. A clue to the diagnosis may be offered in the usually greater irregularity of the vegetations of bacterial endocarditis. The diagnosis must not rest on the culture, *e.g.*, of *Streptococcus viridans*, or of an enterococcus from the lesions, inasmuch as such organisms may be recovered incidentally from cultures of normal valves in a significantly high percentage of cases.³⁸ The diagnosis must be established on the basis of the histologic picture with the weight being given

in pathology, *abnormal* or *diseased condition*, as in *melanosis*, *stenosis*, *varicosis*, etc.

b. A physiological increase or formation (of something specified), as in *chylosis*, *leukocytosis*, etc.

2. In plant pathology, a disease of which a (specified) fungus is the causal agent; a *mycosis*; as in *chytridioidosis*.

Hence, endocardiosis signifies a disease of the endocardium.

particularly to the presence of a destructive or suppurative valvulitis¹⁴ and of *colonies* of bacteria rather than an isolated bacterium here and there.

An even more difficult problem is the differentiation of the few cases of large multiverrucal lesions of degenerative endocardiosis from those of atypical verrucous endocarditis (Libman-Sacks disease, disseminated lupus erythematosus). It may be quite impossible to establish the diagnosis grossly in these instances. Indeed, some of the verrucae of Libman-Sacks disease may be indistinguishable from those of degenerative endocardiosis. As a rule, however, the differentiation may be made by the characteristic interstitial valvulitis and the associated, practically pathognomonic changes in the collagen, especially of the kidney, heart and spleen, which have been recently described in detail.¹³

Relationship of Degenerative Verrucal Endocardiosis to Bacterial Endocarditis

We regard the lesions of degenerative verrucal valvulosis as one of the basic morphologic events in the development of bacterial endocarditis. The fibrinoid material, with certain limitations,⁸ appears to be an attractive medium for the ensnaring and propagation of bacteria present in the general circulation. In principle, this is essentially the point of view of Grant, Wood and Jones,³ who, however, hold the underlying lesion to be a simple thrombus. We feel that the same hemodynamic factors, in large measure responsible for the localization of the initial verruca, operate to bring circulating bacteria in contact with the verruca.^{7, 15} It is our belief that identical principles are concerned in the superimposition of bacteria onto the verrucae of acute rheumatic endocarditis as well as atypical endocarditis (Libman-Sacks disease, disseminated lupus erythematosus). The affinity of the lesions of atypical verrucous endocarditis for bacteria is strikingly illustrated in the occurrence of bacterial endocarditis in fully one-third of the 12 cases described by Klemperer, Pollack and Baehr.¹³ In other words, the verruca of both the specific and nonspecific variety is prone to become a nidus of bacterial proliferation. The details of the evidence for this concept are considered separately.⁸

Healed Lesions of Degenerative Verrucal Endocardiosis

Finally, the evidence indicates that the lesions of degenerative verrucal endocardiosis may heal by fibrosis if the patient survives the illness during which the valvular alteration occurred. As might be expected, it is impossible to distinguish the healed verruca of acute rheumatic disease from that of degenerative endocardiosis. In both instances, the

healed lesion seems to take the form of fibrous tabs such as Lamblian excrescences attached to the corpora arantii or the adjacent ridge of semilunar valves. Similar fibrous prongs may occur on the auriculo-ventricular valves (Fig. 12), or they may take the form of small, smooth nodules or bulbous thickening near the edges of these valves. Such focal fibrous nodules occurring on nonrheumatic valves have been hitherto regarded generally as "senile" or "tension thickenings." It would seem more reasonable, in the light of findings herein presented, to classify them as healed stages of degenerative verrucal endocardiosis.

SUMMARY AND CONCLUSIONS

1. Fifty cases of so-called "terminal endocarditis" or "nonbacterial thrombotic endocarditis" were studied.

2. The valvular lesions of "terminal endocarditis" are characteristically hillocks of degenerated, swollen, *valvular* collagen, occasionally with an admixture of varying amounts of serum, fibrin, platelets and blood cells derived from permeable or eroded vessels of the valves. They are *not* regarded as thrombi deposited onto the valves from the blood within the cardiac chambers, contrary to the generally held impression.

3. It is believed that the lesions are not necessarily "terminal" and that they may occur during the course of a variety of acute and chronic illnesses, many of which are survived with consequent healing of the valvular lesion.

4. The healed lesion, of which the Lamblian excrescence is an example, takes the form of a fibrous tab or nodule, or slight bulbous collagenous thickening near the free edge of the valve (so-called "senile" or "tension thickening"). The healed lesion, by virtue of its projection and consequent hemodynamic disadvantages, is, in turn, prone to undergo recurrent degeneration.

5. The active lesions are, as a rule, primarily degenerative rather than inflammatory.

6. It is suggested that such names as "terminal endocarditis" or "nonbacterial thrombotic endocarditis" are not applicable. The non-specific term, "degenerative verrucal endocardiosis," is offered as being more in keeping with the available knowledge of the lesion.

7. Allergy, vitamin C deficiency, hemodynamic stresses and valvular sclerosis, alone or in combination, may be concerned in the pathogenesis of this nonspecific lesion.

8. Differentiation from acute and recurrent rheumatic valvulitis, bacterial endocarditis, and atypical verrucous endocarditis is usually possible. Gross and microscopic structure, bacterial content, and the

concomitant valvular and extravalvular cardiac lesions must be considered in establishing differentiation.

9. The lesions of degenerative verrucal endocardiosis constitute an important morphologic basis for the development of bacterial endocarditis.

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[Illustrations follow]

DESCRIPTION OF PLATES

PLATE 188

(Figures 1 to 4 illustrate the wide range of patterns assumed by the verrucae of degenerative verrucal endocardiosis.)

FIG. 1. The most common form of degenerative verrucal endocardiosis—the “small, univerrucal” type. The intervening small nodules are possibly the healed, fibrous residuum of verrucae.

FIG. 2. The “large, univerrucal” type of degenerative verrucal endocardiosis occurring in aortic valves showing evidence of old rheumatic inflammation. This lesion is to be differentiated from bacterial endocarditis by histologic examination.

FIG. 3. “Large, multiverrucal” form of degenerative verrucal endocardiosis. From the eroded area of endocardium a verruca had been removed manually. (See Fig. 7 for histologic section.)

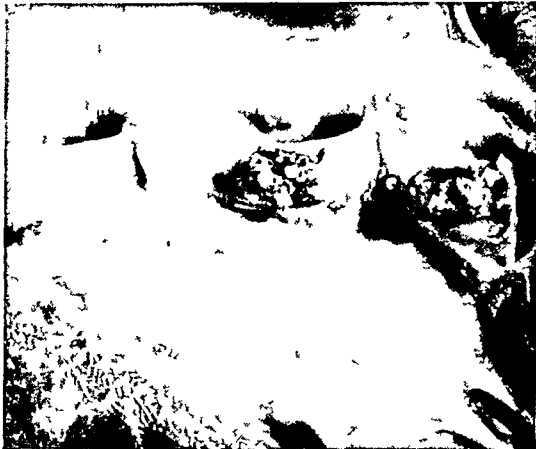
FIG. 4. An unusual example of the “large, multiverrucal” type. This and the preceding form require study of histologic sections for definite differentiation from bacterial endocarditis.

FIG. 5. Lamblian excrescences of aortic valves. These projections from the region of the corpora arantii are regarded as the healed, fibrous stage of verrucae of either degenerative endocardiosis or acute rheumatic valvulitis. The lesions are particularly prone to recurrent degenerative changes because of their exposure to the impact of the blood stream. Very small dentate verrucae may be seen along the valvular ridge. Similar excrescences occur on the mitral and tricuspid valves (see Fig. 12).

FIG. 6. Lamblian excrescences of aortic valves.



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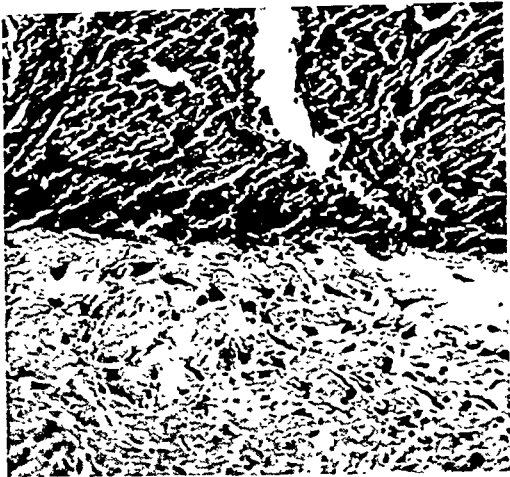
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Degenerative Verrucal Endocardiosis

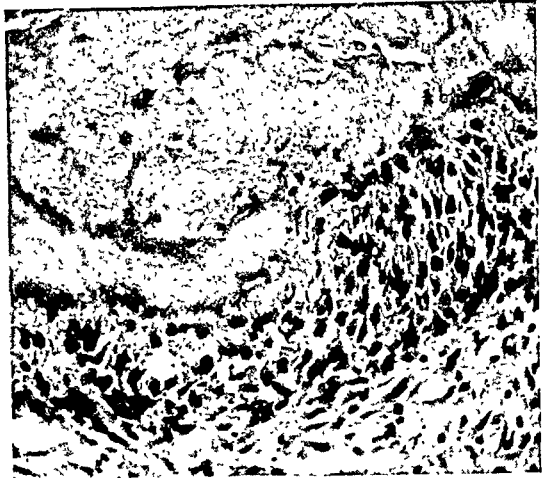
PLATE 189

- FIG. 7. Section of the "exudative" type of degenerative verrucal endocardiosis illustrating the moderate increase in swollen, hyperchromatic histiocytes at the base of the lesion. Section taken from heart illustrated in Figure 3. Hematoxylin and eosin stain. $\times 100$.
- FIG. 8. Section of "exudative" type of degenerative verrucal endocardiosis illustrating the extreme degree of reaction observed. This extensive reaction is seen rarely and only in the "exudative" type of lesions, as shown in Figures 3 and 4. The lesion simulates rheumatic valvulitis but is distinguished by the absence of interstitial valvulitis and of Aschoff bodies. Hematoxylin and eosin stain. $\times 100$.
- FIG. 9. Section of a verruca of degenerative endocardiosis illustrating Anitschkow myocytes (see arrows) in the midst of the fibrinoid material. These cells are not found in cardiac mural or vascular thrombi. Hematoxylin and eosin stain. $\times 500$.
- FIG. 10. Section of a verruca of degenerative endocardiosis illustrating the large foam cells. Hematoxylin and eosin stain. $\times 600$.
- FIG. 11. Low-power view of Figure 10. Foam cells are seen throughout the verruca. Hematoxylin and eosin stain. $\times 16$.
- FIG. 12. Section of fibrous tabs on mitral valve. These are analogous to the Lamblian excrescences of the aortic valves and are regarded as the healed lesion of degenerative verrucal endocardiosis. Hematoxylin and eosin stain. $\times 30$.

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12



Allen and Sirota

Degenerative Verrucal Endocardiosis

PLATE 190

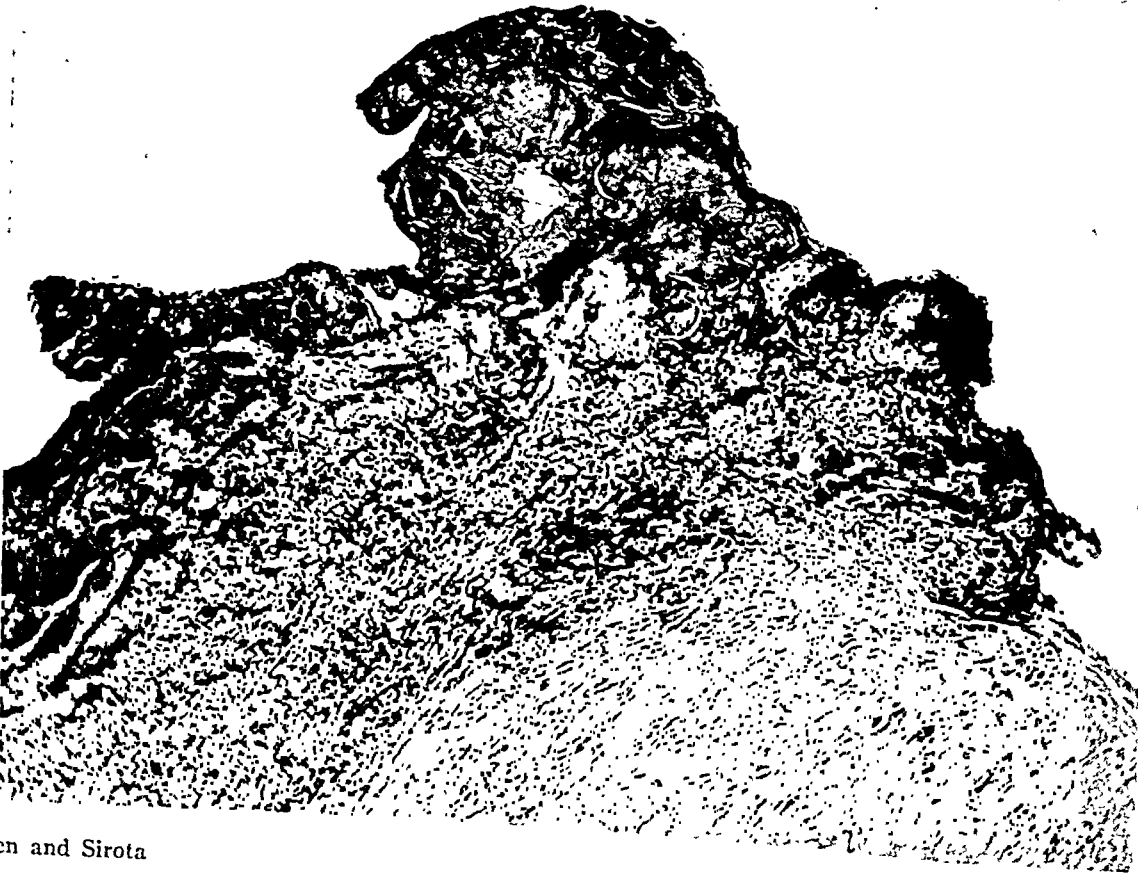
FIG. 13. Section illustrating the pre-verrucal stage of degenerative endocardiosis. The lesion is obviously a valvular degeneration although the left half of it superficially simulates a thrombotic deposit. Hematoxylin and eosin stain. $\times 125$.

FIG. 14. Section illustrating a more advanced stage of verrucal formation. The altered valvular fibrous tissue has swelled to form the irregular knobs of verrucae. There is absence of cellular reaction. This is the "degenerative" type and represents the usual picture of degenerative endocardiosis. Hematoxylin and eosin stain. $\times 100$.

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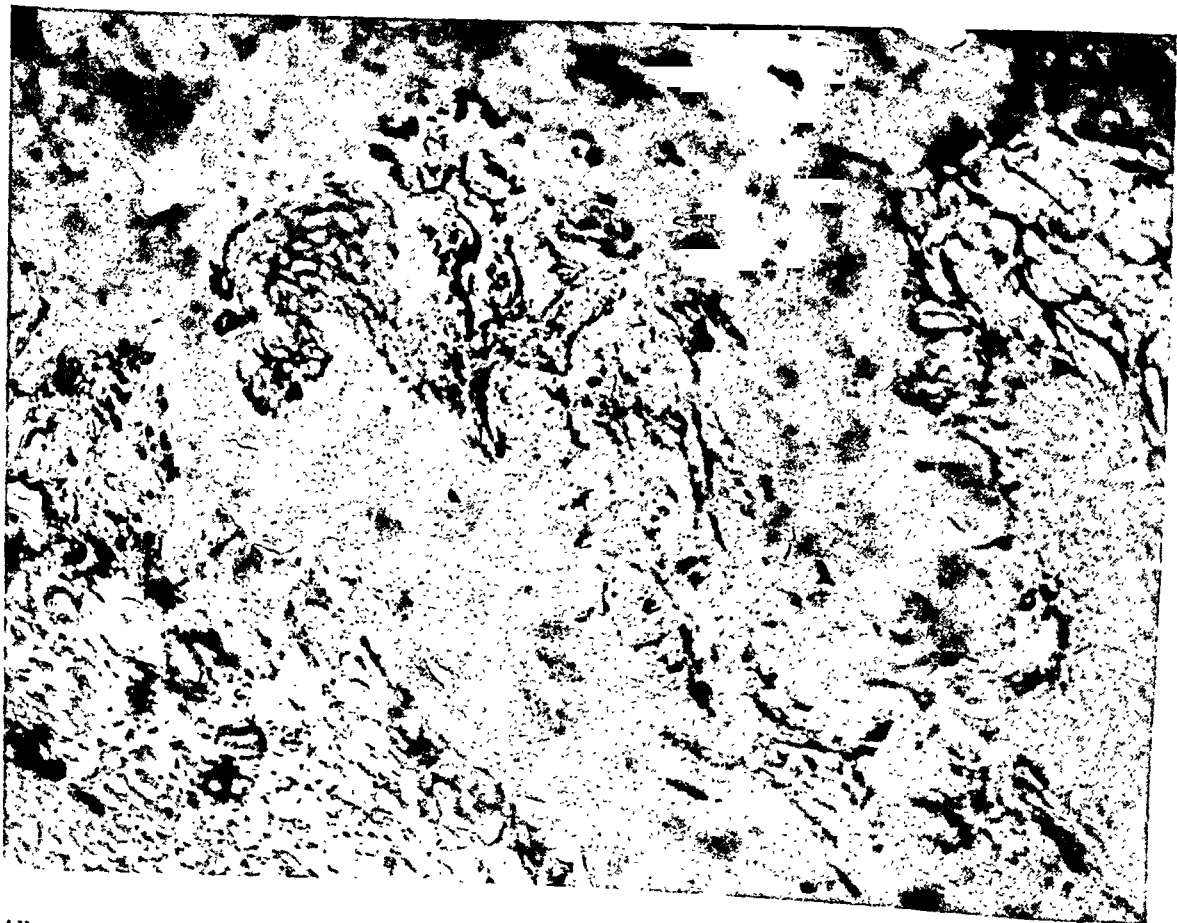
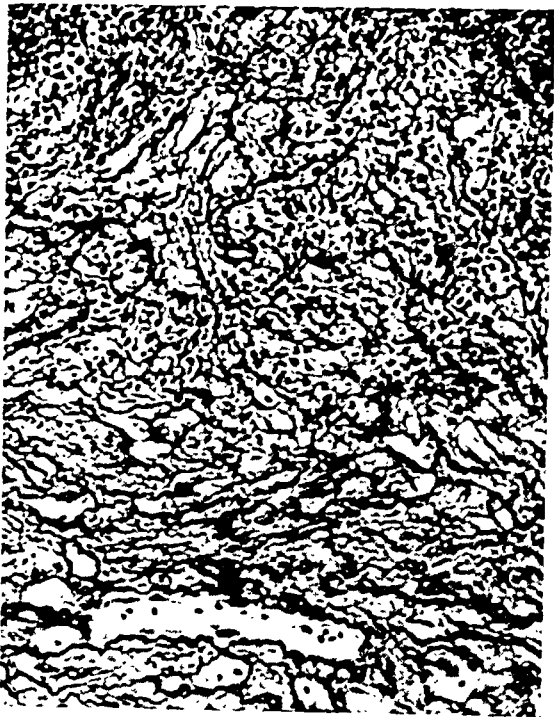
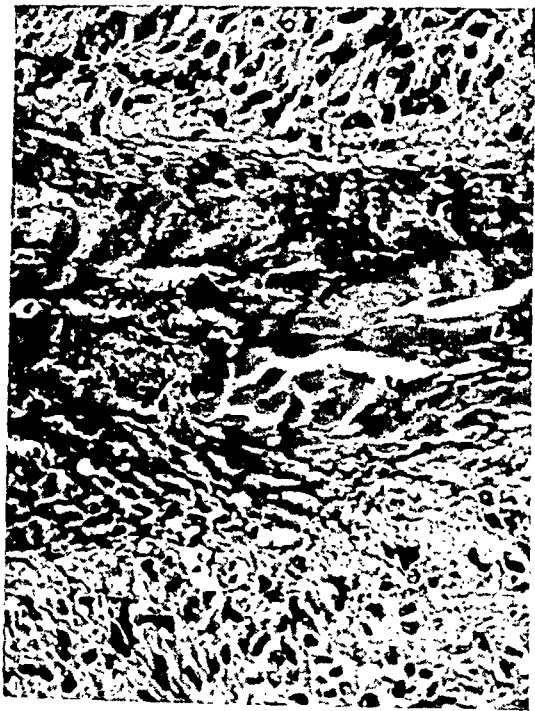
Degenerative Verrucal Endocardiosis

PLATE 191

FIG. 15. Section of granuloma annulare of the skin showing the characteristic periphery of palisaded histiocytes about a core of fibrinoid material that is, without question, altered collagen. Hematoxylin and eosin stain. $\times 260$.

FIG. 16. Section illustrating reticulin in an organizing, mural thrombus. The orderly tracery of argyrophilic fibers contrasts with the irregular pattern in the verruca shown in Figure 17. Silver stain. $\times 200$.

FIG. 17. Section of a verruca of degenerative endocardiosis. The haphazard arrangement of disrupted, anuclear argyrophilic fibers obviously indicates destruction of collagen rather than the organization of a thrombus. There is continuity of the fibers into the homogeneous, platelet-like mass, the latter representing for the most part the more markedly altered collagen. The thickness of the argyrophilic fibers contrasts with the fine reticulin of organizing thrombi (Fig. 16). There is an absence of associated fibroblasts. Silver stain. $\times 200$.



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PLATE 192

FIG. 18. Section of a verruca of acute rheumatic valvulitis to illustrate the similarity in morphogenesis of the verrucae of degenerative endocardiosis and of acute rheumatic valvulitis. The outpouching of the verruca from the valve is well shown and is strongly suggestive evidence against the view that verrucae are thrombotic deposits. $\times 200$.

FIG. 19. Section illustrating recurrent degenerative endocardiosis within a healed verruca. The darker periphery is degenerated collagen—not a thrombotic deposit. Hematoxylin and eosin stain. $\times 100$.

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Degenerative Verrucal Endocardiosis

CHRONIC GRANULOMA ASSOCIATED WITH PERIARTERITIS NODOSA

REPORT OF A CASE WITH RENAL FAILURE *

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The original descriptions of periarteritis nodosa were made by Von Rokitsansky¹ and Kussmaul and Maier.² Reviewing the literature prior to 1938, Harris, Lynch and O'Hare³ found more than 300 cases recorded, and of these 101 were in English publications. From the nature of the case reports, it is evident that the disease is one of protean character. Its widespread manifestations can be explained by diffuse involvement of the arterial system with secondary changes in the tissues supplied by the altered blood vessels. The more common clinical features and the pathologic findings have been carefully studied and described.^{3, 4} A consideration of the etiologic factors and a discussion of recent researches on the experimental production in rabbits of vascular lesions identical with those seen in the human form of the disease have been reported by Rich⁵ and by Rich and Gregory.⁶

The tissue changes secondary to arterial lesions include ischemia, edema, atrophy, hemorrhage, inflammatory infiltration, infarction, necrosis and fibrosis.⁷ There are, however, few descriptions in the literature of widespread granulomatous lesions associated with periarteritis nodosa. In 3 out of 4 cases studied, Neumann⁸ described a peculiar granulomatous reaction containing eosinophils, multinucleated giant cells and zones of radiating necrosis. These lesions were present in the mediastinal tissues, the heart and the kidneys. One of the cases presented by Banowitch, Polayes and Charet⁹ was that of a woman, 35 years old, who had an extensive granulomatous lesion involving the mediastinum, associated with granulomatous foci in many other organs. These lesions consisted of zones of necrosis, fibroblastic proliferation, multinucleated giant cells and cells resembling epithelioid cells.

Because of the nature of the granulomatous reaction which may occur in periarteritis nodosa, the latter should be considered in the differential diagnosis of any chronic granulomatous disease.

The present report concerns an unusual case of the granulomatous variety of periarteritis nodosa with extensive involvement of the kidney producing marked renal insufficiency and death.

REPORT OF CASE

Clinical History. A.H., no. U-67980, a married white woman, 67 years old, was first seen on December 27, 1940. One year before entry she had noted a painless depression on the bridge of her nose and since then had experienced marked crust-

* Received for publication, January 26, 1944.

ing of the nasal mucous membrane and occasional slight epistaxis. She complained of progressive weakness and had lost 27 pounds in weight (56.8 to 44.5 kg.). On many occasions fever of 100° to 101° F. (37.8° to 38.3° C.) was noted. For the past 8 months she had complained of a slight cough with a moderate amount of sputum. Five months before entry she had had an attack of acute parotitis and swelling of the anterior cervical lymph nodes. Examination of one of the parotid glands by biopsy showed "no evidence of malignancy." Three months later the abdomen was explored under general anesthesia. The gallbladder and a small "congenital cyst" of the liver were removed. Histologic examination of the gallbladder revealed "chronic cholecystitis." Blood counts during the 5 months preceding entry showed a moderate leukocytosis and a gradually progressing hypochromic microcytic anemia, which did not respond to treatment with iron or liver. Numerous urinalyses were reported as normal. Roentgenograms of the nose demonstrated that the "saddle" deformity was caused by destruction of cartilage, the nasal bones remaining intact. Roentgenograms of the chest demonstrated very dense hilar shadows with some calcifications in the lymph nodes. Unusually prominent bronchial markings had suggested the presence of interstitial fibrosis.

Physical Examination. The patient was an alert, emaciated, white woman. Temperature, 97.6° F.; pulse, 84 per minute; blood pressure, 155/75 mm. of Hg; height, 166 cm.; weight, 99 lbs. (45 kg.). There was marked wasting of the musculature and subcutaneous tissues. The skin was pale and dry. The scalp was normal; the hair was thin and gray. There were a few small, shotty cervical lymph nodes. The pupils were equal and regular and reacted normally to light and in accommodation. Extra-ocular movements were normal. The retinal arterioles were diffusely narrowed and two small "cotton wool" patches were observed above the right optic disk. The ears and mouth were normal. There was a "saddle deformity" of the nose. The septum was intact, but depressed anteriorly. The nasal mucous membrane was thin and atrophic, and an adherent crusted discharge was present. The thyroid gland was not palpable. The breasts were small, flat and atrophic. The lungs were clear. The heart was not enlarged. An apical systolic murmur was present. The abdomen was scaphoid; none of the abdominal organs were palpably enlarged, and there was a healed right upper rectus scar. Examinations of the pelvis, rectum, nervous system, back and extremities revealed nothing abnormal.

Laboratory Examination. Examination of the blood gave the following data: hemoglobin, 46 per cent (6.3 gm.); erythrocytes, 2.5 million per cmm.; packed cell volume, 20; platelets, 360,000 per cmm.; leukocytes, 13,400 per cmm.; neutrophils, 89 per cent (filamented, 72 per cent; nonfilamented, 17 per cent); eosinophils, 3 per cent; lymphocytes, 8 per cent; icterus index, 5; corrected sedimentation rate, 24 mm. per hour (Wintrobe). Differential cell counts of bone marrow pulp obtained by sternal puncture showed normal maturation of the myelopoietic series and slight suppression of activity of the erythropoietic series. Blood culture and cultures of urine obtained from each kidney showed no growth. Agglutination tests with *Bacillus typhosus*, *B. paratyphosus* A and B, *Brucella abortus* and *Bacillus tularensis* antigens were negative. Tuberculin (1:1000) skin test was negative. Chemical investigation of the blood showed: total serum proteins, 7.53 gm. per cent; albumin, 3.56 gm. per cent; globulin, 3.97 gm. per cent; serum calcium, 10.5 mg. per cent; serum phosphorus, 5.64 mg. per cent; plasma phosphatase, 8.12 mg. of phosphorus by method of Kay and Jenner¹⁰ (normal, 4 to 7 mg.); plasma fibrinogen, 1.25 per cent; nonprotein nitrogen, 75 mg. per cent on January 5, 1941, 102 mg. per cent on January 18; creatinine, 2.7 mg. per cent on January 5, 2.91 mg. per cent on January 18. Blood indican and xanthoprotein reactions were negative. Kolmer and Kahn tests of the blood were negative. The urine was clear and yellow; pH, 5.0; specific gravity, 1.008; faint trace of albumin; sugar, none; occasional

granular casts. The Mosenthal test gave: total day urine, 835 cc.; total night urine, 580 cc.; maximum variation in specific gravity, 0.002. Esbach determination of albumin in the urine indicated 0.8 gm. per liter. With the phenolsulfonphthalein test there was 10 per cent excretion of the dye in 2 hours. An Addis count (12 hour test) gave: erythrocytes, 370,000; casts (all granular), 80,000; leukocytes and epithelial cells, 10,500,000. Roentgenograms of the chest revealed considerable calcification of the aorta. There was over-aeration and fibrosis of both lung fields. The cardiac silhouette was within normal limits.

Course. The temperature varied between 96.0° and 102.5° F. (36.4 to 39.2° C.), the pulse between 80 and 130 per minute and the blood pressure between 155/95 and 105/55. The course of the illness was short; the patient gradually lapsed into coma and expired on January 24, 1941, approximately 1 month after entry to the hospital. A clinical diagnosis of sarcoidosis was made.

Gross Examination

Autopsy was performed 30 minutes after death. Rigor mortis and post-mortem lividity had not appeared. A urinogenous odor was noted when the peritoneal cavity was opened. The latter was normal in appearance except for the presence of firm, fibrous adhesions in the right subhepatic region. The gallbladder was absent. The pleural cavities were normal. There were several firm, fibrous adhesive bands joining the pericardium to the apex and to the anterior left ventricular surface of the heart. The mediastinum was normal in all respects.

The heart weighed 245 gm. It was small and soft. The myocardium, endocardium, heart valves and coronary blood vessels were normal. The right lung weighed 400 gm., and the left, 380 gm. There was slight congestion of both lower lobes and a seropurulent exudate was present within the bronchioles of the right lung. The hilar and mediastinal lymph nodes appeared unaltered.

The liver weighed 1080 gm. There were adhesions on its under surface. The cut surface was normal. The common duct was dilated but not obstructed, and measured 8 mm. in diameter. The spleen weighed 140 gm.; the cut surface was light purple; it appeared moderately hyperplastic.

The right kidney weighed 175 gm. and the left, 180 gm. They presented essentially the same appearance. The capsule was firm, white, fibrous and measured 1.5 mm. in thickness. The capsule was not adherent to the perirenal fat and could be easily stripped from the cortical surface of the kidney (Fig. 1). The surface of the kidney was smooth and showed only a few depressions which appeared to be the remains of fetal lobulations. The cut surface showed a clear differentiation between the cortex and medulla (Fig. 2). The average thickness of the cortex was 0.5 cm. It was extremely firm, fibrous and light yellow. The pyramids were of normal size and light pink, but were poorly striated.

There were no scars, infarcts, hemorrhages, or nodules present. The renal pelves, blood vessels, ureters and bladder were grossly normal.

The gastro-enteric tract presented no abnormalities. The internal genitalia were atrophic. The aorta was atherosclerotic and partially calcified. The vena cava and iliac vessels were not altered.

The thyroid gland was normal in appearance. The adrenal glands were small, the right weighing 4.2 gm. and the left, 2.8 gm. The pituitary gland was normal in size, but contained in its anterior lobe a cyst (filled with clear yellow fluid) which measured 0.5 cm. in diameter. The only lymph nodes of note were a group lying adjacent to the celiac axis. They measured approximately 1.5 by 1.0 by 0.5 cm.; the cut surfaces were normal. The brain weighed 1300 gm. and was normal except for minimal atherosclerotic changes in those vessels comprising the circle of Willis.

Microscopic Examination

Only those tissues involved in the granulomatous process will be described in detail. Other findings of note included bilateral pulmonary congestion, and bronchopneumonia of the right lower lobe. There was atherosclerosis of the aorta, coronary arteries, and mitral and aortic valves.

The most striking alterations were seen in the kidneys. The markedly thickened capsule was composed of dense, hyalinized fibrous tissue, which, with the perirenal fat, was moderately infiltrated with lymphocytes and a few plasma cells, usually arranged around blood vessels (Fig. 3). Practically the entire renal cortical structure, including glomeruli and tubules, was replaced by moderately cellular fibrous tissue, which was densely infiltrated with plasma cells, lymphocytes, and neutrophilic and eosinophilic leukocytes (Fig. 4). The fibrous connective tissue was more abundant in and around the glomeruli.

Few glomeruli were normal; many were entirely replaced by hyalinized fibrous tissue with obliteration of the glomerular space. A few retained small centrally placed glomerular tufts or vascular channels, while others either contained a small central collection of neutrophilic leukocytes or were extensively infiltrated with these cells. Some glomeruli contained small masses of hyaline fibrin, either deposited in glomerular tufts or between the glomerular capsule and the capsular epithelium. Other glomeruli were altered by shrinkage, partial hyalinization or pericapsular fibrosis.

The few tubules remaining in the fibrotic cortical zone occurred singly or in scattered groups. The convoluted tubules were dilated and hypertrophied, and showed cloudy swelling and minimal fatty degeneration of their lining cells. The solitary tubules were lined by flattened

atrophic epithelium and contained colloid, purulent material, or a combination of the two. The tubules became more numerous toward the medullary portion of the kidney; the collecting tubules in the renal pyramids were normal, although the interstitial fibrous tissue in this region was abundant, hyalinized and slightly infiltrated with lymphocytes, neutrophilic leukocytes and plasma cells. Toward the pelvis, the inflammatory reaction was minimal.

The altered renal cortex was quite avascular. The few small arteries and arterioles present appeared normal. The larger arteries (arciform) of the corticomedullary region presented a subintimal proliferation of fibrous tissue with secondary hyaline degeneration. There was thickening, irregularity and reduplication of the internal elastic membrane. The external elastic membrane was thick and well defined. Evidences of active arteritis were absent.

The epidermal layer of the nasal mucous membrane was atrophic. The submucosa was fibrotic, almost avascular and densely infiltrated with neutrophilic leukocytes, lymphocytes, macrophages and plasma cells. In the deeper layer of the submucosa was a large artery having a thick, almost acellular, hyalinized fibrous tissue wall (Fig. 5). The lumen was represented by a narrow, endothelium-lined cleft which was surrounded by a folded, hyalinized, fragmented, elastic tissue membrane. Inflammatory cells were present at the periphery but not within the wall of the vessel.

The entire posterior lobe and part of the intermediate and anterior lobes of the pituitary gland were involved in a granulomatous process composed of fibrous tissue, densely infiltrated with the same varieties of inflammatory cells as were present in the kidneys (Fig. 6). The neutrophilic leukocytes were grouped in small, rounded foci. In the less involved portions of the posterior lobe and in the capsule, the inflammatory cells were distributed in a perivascular arrangement. The majority of the blood vessels were not altered. A few presented mild edema of the media.

Re-examination of the specimen of the parotid gland obtained 5 months before death showed diffuse replacement of the glandular tissue and interlobular fat by cellular fibrous tissue, infiltrated with plasma cells, lymphocytes, and smaller numbers of neutrophilic and eosinophilic leukocytes (Fig. 7). Some of the ducts and acini showed epithelial degeneration and desquamation and contained a few inflammatory cells. Minimal hyaline thickening was the only alteration noted in the few blood vessels present.

Microscopic examination of the liver at autopsy showed it to be essentially normal. The portions removed surgically 2 months before death contained a longitudinal segment of a large vascular channel. Be-

cause of its large diameter and location at the anterior edge of the liver, this structure undoubtedly represented a small aneurysm. The vessel was partially lined by a layer of low cuboidal endothelial cells; one segment was completely occluded by dense hyalinized connective tissue and presented a folded, dense, eosinophilic wall. An adjacent portion was partially occluded by loosely arranged, newly formed, cellular fibrous tissue containing many inflammatory cells, including lipid-filled macrophages. The vessel wall consisted of a thick layer of hyalinized fibrous tissue which contained the remaining irregular fragments of the elastic membrane, and a mild infiltration of lymphocytes and neutrophilic leukocytes. The vasa vasorum were partially or completely occluded by connective tissue and had perivascular collars of lymphocytes and neutrophilic leukocytes. A large blood vessel in the adjacent parenchyma was the site of an active inflammatory process with a diffuse infiltration of the vessel wall by lymphocytes, plasma cells, and neutrophilic and eosinophilic leukocytes (Fig. 8). The lumen was represented by a small, endothelium-lined cleft surrounded by large, young fibroblasts, acute inflammatory cells and small masses of fibrin.

All tissues involved in the granulomatous process were stained with the Glynn modification of the Gram stain, Ziehl-Neelsen carbolfuchsin and the Levaditi stains. No acid-fast organisms or spirochetes were found in any of the sections. Thorough search was made for *Histoplasma capsulatum* with negative results. In the submucosa of the nasal mucous membrane there were numerous gram-positive cocci in groups and in short chains, and a few short gram-negative bacilli. Bacteria were not observed elsewhere.

SUMMARY

The case presented is that of a woman, 67 years old, who had suffered for almost a year from weakness, fever, anemia, weight loss, cough, sputum, and crusting of the nasal mucous membranes, and whose death was due to renal insufficiency. During the course of her illness she developed transient swelling of the parotid glands and anterior cervical lymph nodes. She was found to have atrophic rhinitis with a "saddle" deformity of the nose. The retinal arterioles were narrowed and several small patches of "cotton wool" exudate were observed. The blood pressure was not elevated and no symptoms of renal insufficiency were present until uremia supervened late in the course of the disease. However, tests of renal function during the last month of the patient's illness showed azotemia, hyposthenuria, slight albuminuria and marked impairment of excretory function. The Addis count showed only a

slight increase in granular casts, leukocytes and epithelial cells, and the xanthoprotein and indican reactions curiously were negative. At autopsy there was found a chronic granulomatous inflammatory process, which had practically replaced all of the functional renal cortical parenchyma and had likewise involved the nasal cartilage and septum, the posterior lobe of the pituitary gland, the parotid gland and a small portion of the liver. Numerous vascular lesions corresponding to periarteritis nodosa were found, the majority of which were histologically healed. The renal vessels, a nasal artery and most of the glomeruli showed evidences of a healed process. In a few glomeruli there was active glomerulitis. Active arteritis with aneurysm formation was demonstrated in tissue taken for biopsy from the liver 2 months before death.

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[Illustrations follow]

DESCRIPTION OF PLATES

PLATE 193

FIG. 1. External surface of left kidney demonstrating the thickened capsule and the smooth cortical surface after stripping. $\times 3/5$.

FIG. 2. Cut surface of left kidney showing pallor of cortex with well preserved corticomedullary differentiation. $\times 3/5$.

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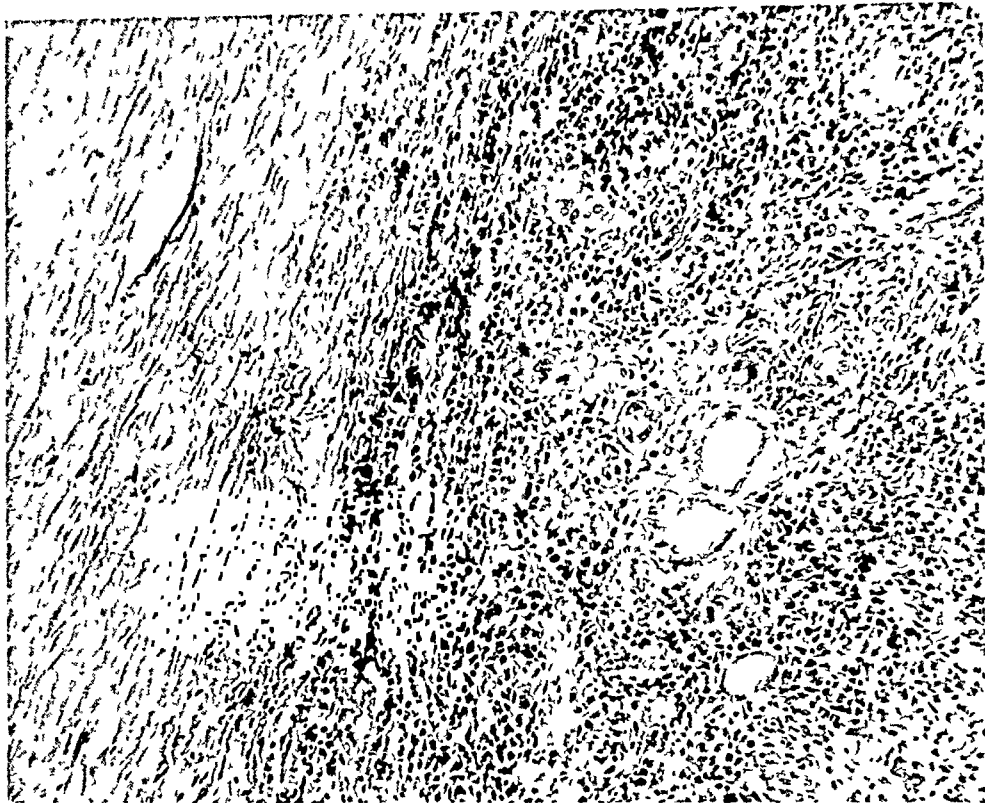
Granuloma with Periarteritis Nodosa

PLATE 194

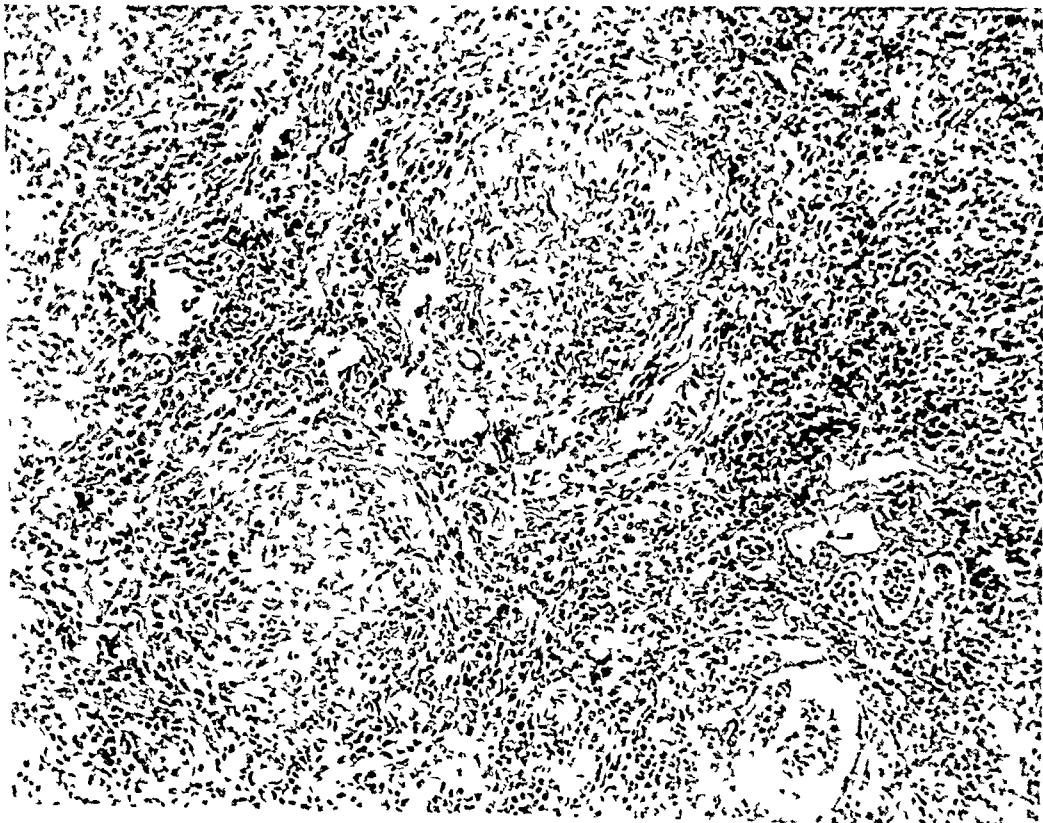
FIG. 3. Thickened renal capsule with adjacent cortex. Hematoxylin and eosin stain. $\times 120$.

FIG. 4. Renal cortex, demonstrating replacement of glomeruli and tubules by the chronic granulomatous reaction. Hematoxylin and eosin stain. $\times 120$.

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Granuloma with Periarteritis Nodosa

PLATE 195

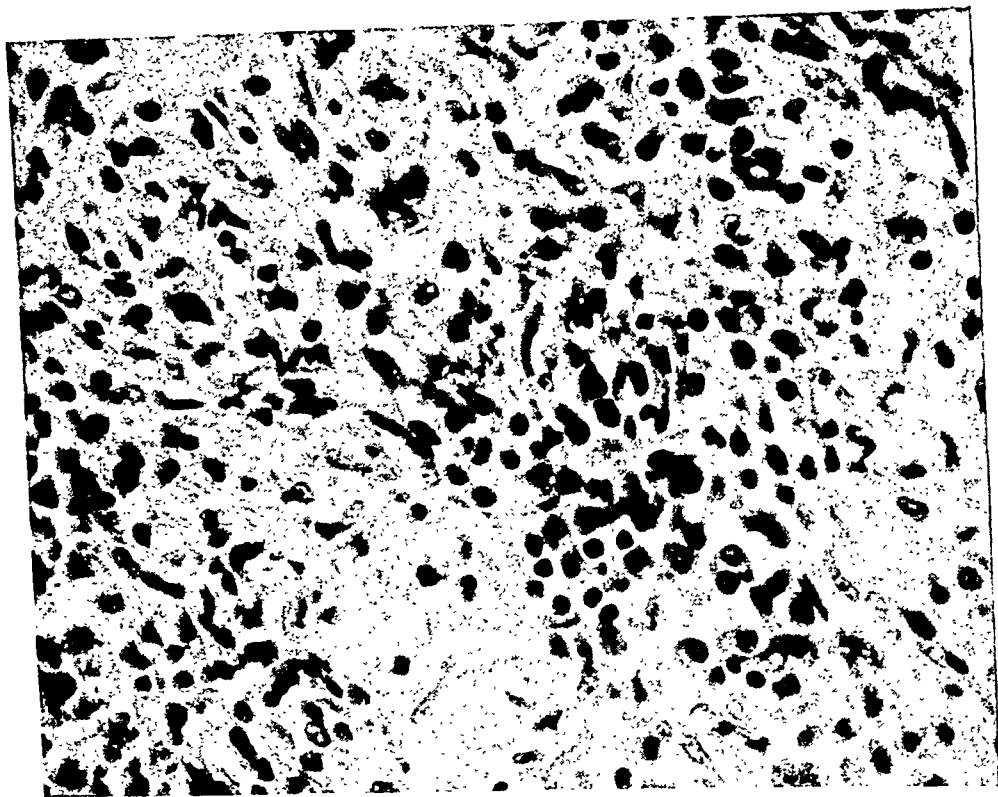
FIG. 5. Thickened artery in the submucosa of the anterior nasal cavity. The internal elastic membrane is present. Weigert's elastic tissue and van Gieson's stains. $\times 120$.

FIG. 6. Posterior lobe of pituitary gland, with replacement of the normal glial structure by chronic inflammatory tissue. Hematoxylin and eosin stain. $\times 300$.

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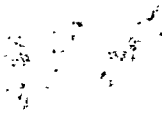
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Granuloma with Periarteritis Nodosa

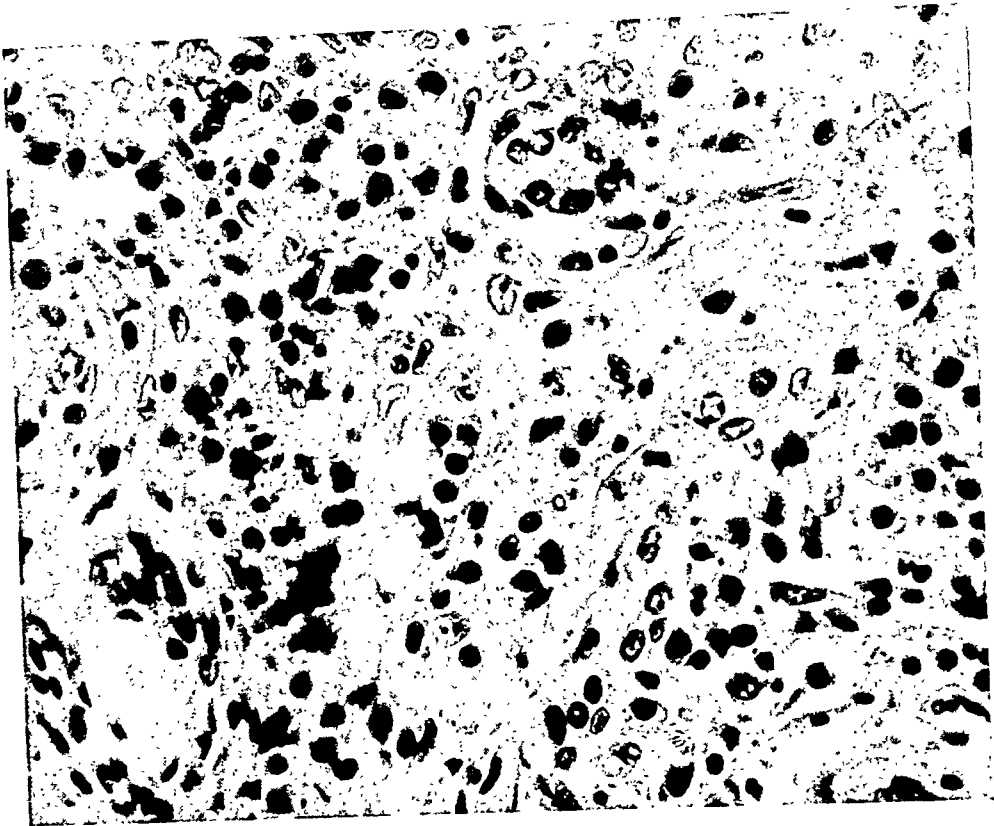
PLATE 196

FIG. 7. Parotid gland, showing replacement of most of the glandular tissue by fibrous tissue and inflammatory cells. Hematoxylin and eosin stain. $\times 300$.

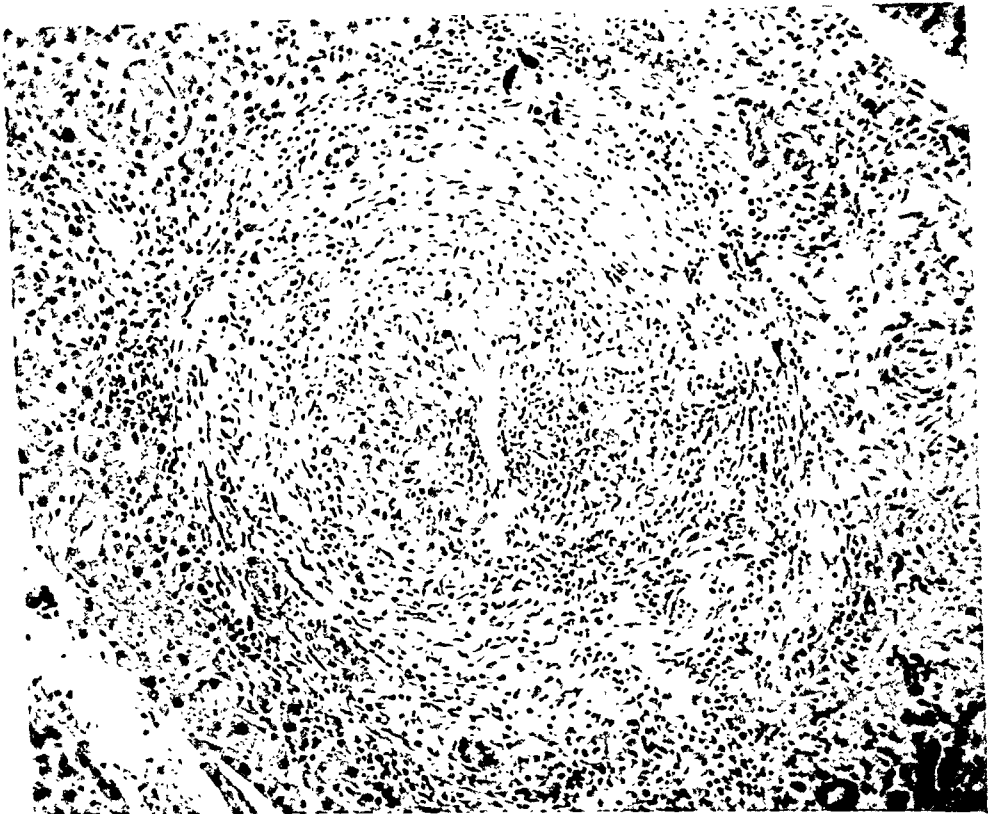
FIG. 8. Section of an hepatic artery near the small aneurysm, showing destruction of the vessel wall and replacement by connective tissue and inflammatory cells. Hematoxylin and eosin stain. $\times 120$.



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† Abstract of paper presented at the meeting of The American Society for Experimental Pathology held at Chicago, Illinois, April 17, 18 and 19, 1941.

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